



# MODERN ORGANIC CHEMISTRY

BY

CHARLES ALEXANDER KEANE, D.Sc., Ph.D., F.I.C.

PRINCIPAL, AND HEAD OF THE CHEMISTRY DEPARTMENT,  
THE SIR JOHN CASS TECHNICAL INSTITUTE, LONDON.

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## PREFACE.

IN a letter to Berzélius in 1837 Wöhler, in describing the condition of organic chemistry, says—"It seems to me like the tropical forest primæval, full of the strangest growths, an endless and pathless thicket, in which a man may well dread to wander."

During the long period that has elapsed since these words were written, this branch of chemistry has changed to one of the most thoroughly investigated and systematic of sciences, but its development has been associated with so much technical detail, both in language and in method, that Wöhler's words still express the view of many readers and workers in other sciences on the organic chemistry of to-day.

The causes that contribute to this opinion are not far to seek. The necessity of separating the study of carbon compounds from that of the other elements, which has arisen purely for the sake of convenience, and which led to the division of chemistry into organic and inorganic, has tended to relegate the former to the position of a branch of the science which is reserved for the specialist. This division is in many respects unreal and disadvantageous; it has, to a considerable extent, had the effect of robbing organic chemistry of its true position as an intrinsic part of chemical science as a whole, a position which it fully merits on account of its important contributions to chemical theory and to technology.

Further, the very technical character of the language of organic chemistry has undoubtedly proved a barrier to its more general study on the part of many who would

otherwise have followed its wide-reaching developments with interest. The existence of such a barrier must to some extent be admitted, but it is far less formidable than is generally imagined. Owing to the importance attached in this branch of chemistry to the study of what is termed the "structure" of compounds, the elementary principles of the subject appear somewhat more complex than those of inorganic chemistry; they can, however, be acquired with a little careful study, and the apparently intricate formulæ and nomenclature then become helpful, systematic and explanatory. In short, the language is easily learnt, and with this knowledge the full story of organic chemistry is open to all.

There can be but few workers in science to whom organic chemistry is not of importance or even of direct value. The physiologist, the biologist and the medical practitioner are continually concerned with substances and processes that are included in the domain of organic chemistry, whilst the physicist, the engineer, and the geologist are brought into touch with organic compounds both in practice and in research. In view of the many applications and materials of organic chemistry that enter into the daily life of the individual the subject is one that should also appeal to the general reader of science, and especially so because its field of study is so closely concerned with the fundamental substances and processes of life.

It is with the object of making some knowledge of organic chemistry accessible to students of other sciences and to the general reader, that this volume has been written. No attempt has been made to make it a complete survey of the progress of the science; the scope of organic chemistry is far too wide to allow of any approach to this within the limits of a small volume, and many subjects of interest and importance have, of necessity, been omitted. The aim has been restricted to recording

some of the methods and problems of organic chemistry and to giving some account of the lines along which its present scientific and technical importance has developed. The work is, therefore, in no sense a text-book, but rather the complement of one, and the plan of treatment is, in many respects, entirely different from that which is best adapted to the systematic study of the science.

In order to render the subject matter as easy of approach as possible every attempt has been made to render the stepping stones to the general principles and technicalities of organic chemistry clear and concise, and to illustrate the methods and applications of the science by simple and typical examples. It is impossible to give a satisfactory account of the subject without recourse to formulæ and occasionally to long names, but in mitigation of the number of "strangest growths" that may appear to overburden the pages at times it may be stated that a special effort has been made to arrange the material dealt with in such a way that the same examples have been made use of, as far as practicable, as the basis for the discussion of the various problems brought under consideration.

It is accordingly hoped that the contents will be accessible to all who have at some time or other acquired a knowledge of elementary chemistry; also, that some of the later and more special chapters may prove helpful to students of chemistry. Reference to the ordinary text-books of organic chemistry will supply others with the technical details omitted, or only touched upon, in the book.

A chapter on "The Laboratory Methods of Organic Chemistry" has been included, which may serve to give an insight into the ways and means employed in the practice of organic chemistry.

The choice of references has been restricted to what may be regarded as the classical investigations in the

science and to modern work and discoveries of general importance; a number of quotations from the former are given which may add the factor of a personal interest in those who have laid the foundation stones of this branch of chemistry.

I desire to record my debt of thanks to those who have helped me in this attempt to tell something of the present field of modern organic chemistry. These are due to Dr. A. N. Meldrum, who very kindly read through the whole of the manuscript and who gave much valuable criticism, and to Dr. R. C. Farmer for his help and suggestions in the revision of the proofs; also to Prof. Sydney Young, F.R.S., and Prof. F. E. Francis, who revised the chapters on "The melting point and boiling point of organic compounds" and "Isomeric change and dynamic isomerism," respectively. I have further pleasure in thanking Messrs. Baird & Tatlock and Messrs. Archibald Constable & Co. for the loan of blocks.

CHARLES A. KEANE.

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# LIST OF ABBREVIATED TITLES OF JOURNALS.

JOURNAL.	ABBREVIATION.
Annalen der Chemie - - - -	Annalen.
Annales de Chimie et de Physik - -	Ann. Chim. Phys.
Berichte der deutschen chemischen Gesellschaft	Berichte.
Bulletin de la Société chimique de Paris -	Bull. Soc. Chim.
Chemiker Zeitung - - - -	Chem. Zeit.
Chemisches Centralblatt - - - -	Chem. Centr.
Comptes rendus hebdomadaires des Séances de l'Académie des Sciences - - - -	Comptes rend.
Journal für praktische Chemie - - - -	J. prakt. Chem.
Journal of the American Chemical Society -	J. Amer. Chem. Soc.
Journal of the Chemical Society - - - -	J. Chem. Soc.
Journal of the Chemical Society, Abstracts -	J. Chem. Soc. Abstr.
Journal of the Chemical Society, Proceedings -	Proc. Chem. Soc.
Journal of the Royal Society of Arts - - -	J. Soc. Arts.
Journal of the Society of Chemical Industry -	J. Soc. Chem. Ind.
Monatshefte für Chemie der kaiserlichen Academie der Wissenschaften. Vienna	Monatsh. Chem.
Philosophical Magazine and Journal of Science	Phil. Mag.
Philosophical Transactions of the Royal Society -	Phil. Trans.
Proceedings of the Royal Society - - - -	Roy. Soc. Proc.
Zeitschrift für angewandte Chemie - - - -	Z. angew. Chem.
Zeitschrift für physikalische Chemie - - -	Z. physik. Chem.
Zeitschrift für physiologische Chemie - - -	Z. physiolog. Chem.



# MODERN ORGANIC CHEMISTRY.

## CHAPTER I.

### THE HISTORICAL DEVELOPMENT OF ORGANIC CHEMISTRY.

The foundation of Organic Chemistry as a science—The scope of modern Organic Chemistry—The division of chemistry into Organic and Inorganic in reference to the historical development of Organic Chemistry—The “vital force” distinction—The synthesis of organic compounds—Organic Chemistry the chemistry of the carbon compounds.

ALTHOUGH a distinction had been drawn between organic and inorganic chemistry as early as the latter half of the seventeenth century, practically no progress was made in the study of organic compounds until the nineteenth century; indeed, the scientific foundation of the subject can, with full justice to the work of the previous years, be dated from 1832, when Liebig and Wöhler published their classical memoir *Investigations on the Radical of Benzoic Acid*.<sup>1</sup> Their own introductory words are the best evidence of the value and originality of their work. “We may congratulate ourselves,” they say, “if we succeed in clearing a narrow path through the dark domain of organic nature, which appears to us as one of the avenues which may perhaps lead to the true method of investigating and knowing this region, although we are well aware of its illimitable extent. Nor, indeed, can we as yet reasonably expect to arrive at any very profound or

<sup>1</sup> “Untersuchungen ueber das Radical der Benzoesäure,” Liebig and Wöhler. *Annalen*, 1832, iii., 249. Republished 1891, Ostwald's *Klassiker der exacten Wissenschaften*, No. 22.

wide generalisations, owing to the absence of previous investigations, as well as to the difficulty of obtaining the necessary materials. We ask you to regard the following experiments from this standpoint; as far as their extent and connection with other branches of investigation is concerned, they leave a wide and fruitful field for research."

In this investigation it was proved that oil of bitter almonds, benzoic acid, and a number of compounds obtained from them may all be regarded as containing a group of atoms which made the recognition of their mutual relationship possible. This group, or "*Zusammengesetzter Grundstoff*," as it was called, played the part of an element; it was the characteristic constituent of a series of compounds. Owing to its compound nature (it contains carbon, hydrogen, and oxygen) it was regarded as a *compound radical*.

A new era in organic chemistry was awakened by this work. Although numerous compounds derived directly or indirectly from the animal and vegetable kingdoms were previously known and their composition ascertained, their relation one to another was in no way understood. Their relative complexity, as compared with the compounds found in mineral or inorganic chemistry, had been recognised some fifty years before by Lavoisier, and some attempt had been made, especially by Berzelius, to show the relationship of their constituent parts. But such relations were essentially hypothetical, they were not based on experiment. The great advance marked by Liebig and Wöhler's work was that they founded their theoretical conclusions on experimental data.

A clear insight of the genealogy of one group of substances having been once obtained, it was not long before similar relationships were discovered amongst other, already well-known compounds. Dumas and Liebig succeeded in showing that many groups of organic compounds were characterised by containing the same groups of atoms or radicals, and thus much of the accumulated experimental material of organic chemistry was brought into line and systematised. These radicals came to be regarded as so characteristic of organic compounds that it was at one time proposed to define organic chemistry as "the chemistry of the compound radicals."

Both from a theoretical and from an experimental standpoint the researches of Liebig and Wöhler gave an immense stimulus to the study of organic chemistry. The "field for research" opened out by their investigations has proved "wide and fruitful" far beyond anything these founders of the science could have hoped for. The growth of organic chemistry has been extraordinary; and although a specialised branch dealing with the compounds of but few elements, it now occupies more attention amongst investigators than the whole of inorganic chemistry.

Its growth has not consisted merely in the preparation of a vast number of more or less complex compounds; it has been far more than this. Definite relationships between the numerous groups of substances have been thoroughly studied; the variations in physical and physiological properties that accompany changes in the chemical nature of substances have been worked out, so that despite the immense number of compounds that are now included under the head of organic chemistry, the subject rests on a thoroughly systematic basis. The stepping-stones that lead up from the simpler to the more complex substances are gradual and well defined, and the accuracy of this knowledge has added many new and important truths to the whole range of chemical science.

Organic chemistry supplied the facts on which the right interpretation of the relation of atoms and molecules was founded, some fifty years ago. About the same time Frankland and Kekulé established the all-important doctrine of the valency of the elements from the study of organic compounds, and within the last twenty-five years organic chemistry has especially developed a knowledge of the spatial arrangement of the atoms of molecules.

The developments of organic chemistry have brought it into close contact with many kindred sciences. Physiology and pharmacology, biology, pathology, and forensic medicine have recognised organic chemistry as an indispensable helpmate, whilst in return they have pointed out many new fields of work. Such work is still in its infancy; it is work lying chiefly on the borderland of two sciences, and is likely to be best developed by the combined efforts of workers in the correlated subjects.

Applied science also is largely indebted to organic



chemistry. The aniline colour industry, fermentation industries, the manufacture of soap, candles, and explosives, of many medicines and foods are founded upon and have been developed by the study of organic chemistry. In all these industries pure and applied science have worked together most successfully to their mutual advantage.

Such is the field of modern organic chemistry, one of far-reaching influence and great promise, full of life and vigour, and destined to reveal its full share of the workings of Nature.

*The Division of Chemistry into Organic and Inorganic, in reference to the Historical Development of Organic Chemistry.*—The classification of chemical substances according to their origin from “the three kingdoms of Nature” is first met with in Nicolas Lemery’s famous *Cours de Chymie*, a book which passed through thirteen editions, and which was translated into no fewer than five languages. It was published in 1675. Lemery’s classification, which was generally accepted by the chemists of the phlogiston period, consisted of the following three divisions:—

1. *Mineral Substances.*—Such as metals, minerals, earths, and stones.

2. *Vegetable Substances.*—Such as plants, resins, gums, fruits, juices, and honey.

3. *Animal Substances.*—Such as various parts of the animal body and excrements.

No fundamental differences or similarities were recognised amongst the members of these three groups, but Becher (1635-82) pointed out that, whilst the same elements occurred in the three divisions, they were combined with each other in a simpler manner in the case of mineral substances than in animal and vegetable products, and Stahl (1660-1734) clearly recognised the preponderance of what he called the “aqueous and combustible principles” (hydrogen and carbon) in the two latter groups.

Towards the close of the eighteenth century, and after Lavoisier had overthrown the treasured phlogiston theory of his predecessors, a number of substances of vegetable and animal origin were prepared. Scheele (1742-86) isolated and distinguished many of the commoner organic acids, and by the decomposition of oils and fats obtained glycerine, “Scheele’s sweet principle.” Rouelle (1703-70)

investigated several animal products and discovered, amongst other substances, urea and hippuric acid.

Lavoisier (1743-94) directed his attention to these new compounds. He first recognised the necessity of finding out what their constituent elements were, and of investigating their relationship to the then more completely understood mineral products, which included many substances prepared in the laboratory. He found that three elements, carbon, hydrogen, and oxygen, were the essential constituents of vegetable products, and that these same three elements, generally accompanied by nitrogen and sometimes by phosphorus and sulphur, were characteristic of all substances of animal origin. It was recognised later<sup>1</sup> that other elements could enter into organic compounds, but carbon always formed an essential part of such compounds. Further, Lavoisier realised the greater complexity of animal and vegetable as compared with mineral products; but most important of all, he recognised the fact that the general laws of chemical combination were equally applicable to all the three groups. His classical investigation on the fermentation of sugar showed that the quantity of alcohol and of carbon dioxide formed was regulated by the amount of sugar decomposed, just as when he heated mercury in the air the quantity of oxide of mercury formed depended upon the volume of air present. From analysis he found that these vegetable and animal products were definite and unvarying in their composition, and he proved by direct experiment that in the changes they undergo there is a simple quantitative relationship to their decomposition products.

Berzelius (1779-1848), the great Swedish chemist whose classical determinations of the atomic weights of many of the elements still rank amongst the standard values, greatly improved the methods for the analysis of substances of organic origin—*i.e.*, the methods for the determination of carbon, hydrogen, and nitrogen. His numerous analyses, especially of the salts of organic acids, entirely confirmed Lavoisier's earlier views, and proved that both in their composition and in the products of their decomposition these substances followed the fundamental laws of chemical combination. He also showed that

<sup>1</sup> Gmelin, *Handbuch der Chemie*, 1848, iv. 3.

organic compounds, like inorganic, obeyed the law of multiple proportions, and, therefore, that their composition rested equally securely on the atomic theory of chemical compounds.

The similarity of the compounds derived from the vegetable and animal kingdoms, especially in respect to the elements composing them, led in the early years of last century to the division of chemical compounds into inorganic and organic. This division was, however, not worked out in any detail, and at first no definite mark of distinction separated the two groups. Indeed, as late as 1817 Gmelin stated in his handbook that "the difference is one that could be more easily felt than defined"; it had evidently no scientific basis. But very shortly afterwards a sharp line was drawn between the two groups, both by Gmelin and by Berzelius. They pointed out that whereas inorganic compounds could be built up in the laboratory from their constituent elements, this was not possible with organic substances. These latter were believed to be a product of Nature; natural forces alone could lead to their formation, and to call these forces into play was entirely beyond the powers of the chemist. This idea of a *vital force* remained the barrier between organic and inorganic substances for many years. It has fallen now, but it held its ground for a long time, yielding only to an ever-growing army of well-ascertained facts. In 1776 Scheele had obtained oxalic acid by oxidising sugar, and Doebereiner prepared formic acid from tartaric acid in 1822; but the first attack to receive the general attention of chemists came in 1828, when Wöhler prepared urea from ammonium cyanate, a substance regarded as essentially inorganic, although it had not then been prepared from its elements. Since, however, urea is very easily decomposed into carbon dioxide and ammonia, it was argued that although a product of animal metabolism, it was not a typical organic substance, and that the preparation of the more complex and strictly organic compounds was still impossible. In the same year Hennell<sup>1</sup> showed that alcohol could be prepared from olefiant gas (ethylene), and this discovery must share with that of Wöhler the distinction of being one of the first instances of the preparation of an organic compound in

<sup>1</sup> *Phil. Trans.*, 1828, p. 365.

the laboratory. At the time, however, alcohol was not looked upon as a vital product in the same sense as urea, and Hennell's discovery did not, in consequence, arouse the same interest as that of Wöhler; nor has it received full acknowledgment until recently.<sup>1</sup> In neither instance were the products obtained built up *ab initio* from the constituent elements, for Hennell started from ethylene prepared by the action of heat upon oil, and the ammonium cyanate used by Wöhler was derived from a cyanide prepared from nitrogenous organic matter; in this respect the two preparations stand on an equality, but they are both to be regarded as amongst the first proofs that organic products, like inorganic, could be prepared in the laboratory.

In 1845 Kolbe prepared acetic acid by a somewhat complex reaction from carbon bisulphide and chlorine, and by 1860, when Berthelot published his *Chimie organique fondée sur la Synthèse*, this building up, or *synthesis*, of organic compounds had completely demolished the old distinction between the two branches of chemistry. Such syntheses are no longer restricted to the more simple substances, such as ethylene, alcohol, or formic acid, which Berthelot prepared by simple and direct processes from the constituent elements; complex compounds like alizarin, the colouring matter of madder, indigo, grape sugar, and even some of the complex vegetable alkaloids, such as conine, piperine and nicotine, have been prepared by purely synthetical reactions. There are certainly still many substances in the vegetable and animal kingdoms which so far have defied the onslaughts of the organic chemist, but what has been accomplished is the surest indication that these too must sooner or later yield their secret. The first step in such work is to ascertain the products which can be obtained by carefully breaking down the complex substances into simpler compounds, and thus to find out the way in which their molecules are built up; their synthetical preparation then soon follows, and sufficient has been done in this direction to point to the probability of synthetical methods for the preparation of compounds like quinine, morphine, and glucosides being fairly within sight. Methods for the

<sup>1</sup> Cf. Meldola, *British Association Reports*, 1895, p. 649.

investigation of far more complex products, such as proteins and ptomaines, are as yet comparatively in their infancy, but a promising beginning has been made, although much work is undoubtedly necessary before their preparation in the laboratory is likely to be realised; such realisations, however, require advances probably neither greater in kind nor in degree than those already achieved.<sup>1</sup>

*The Synthesis of Organic Compounds.*—Whilst the synthesis of organic compounds has entirely overthrown the old idea of a “vital force,” it is important to bear in mind that the methods employed for the building up in the laboratory of the compounds obtained from Nature are not necessarily those followed by Nature herself. The laboratory processes at present known are, in fact, seldom if ever identical with those that occur in plants and animals, and one of the widest and most important fields of inquiry that still awaits investigation is the study of the sequence of changes that result in the natural formation of animal and vegetable products. It may be that life is necessary for the production of compounds as they are produced by Nature, and that such natural synthesis is in consequence dependent upon a vital force. This has yet to be proved or disproved, but at present the old idea of a vital force, with a more restricted meaning, is still a characteristic of naturally occurring organic compounds, though it is no longer one which can separate organic from inorganic chemistry. “Natural syntheses” are characterised by the fact that they take place at the ordinary temperature; also it is to be recognised that vital products may be the result either of a building up, or up-grade synthesis from simpler materials, or of a breaking down or

<sup>1</sup> Literature on the history of organic chemistry:—

Schorlemmer, *The Rise and Development of Organic Chemistry*. Revised by Smithells; 1894.

E. von Meyer, *History of Chemistry*. Translated by M'Gowan. Third edition; 1906.

Kopp, *Geschichte der Chemie*; 1843-47. *Entwicklung der Chemie in der neueren Zeit*; 1873.

Kekulé, *Lehrbuch der organischen Chemie*; 1859.

Ladenburg, *Lectures on the History of the Development of Chemistry since the time of Lavoisier*. Translated from the second German edition by Leonard Dobbin; 1900.

## HISTORICAL

down-grade synthesis from more complex molecules.<sup>1</sup> To what extent such bio-chemical changes can be imitated in the laboratory by purely chemical means remains to be established; it is very probable that the chemist can learn much of their nature by calling to his aid either life itself, or the more immediate products of life in the study of chemical changes. Some work has already been done in this direction, and an indication of its value is afforded by the fact that certain up-grade syntheses can be effected by means of enzymes, which are not at present possible with ordinary chemical reagents.<sup>2</sup>

*Organic Chemistry the Chemistry of the Carbon Compounds.*—The old line of demarcation between organic and inorganic chemistry having been thus removed, the difficulty of defining the province of the former again appeared. The fact that the same laws obtain amongst organic and inorganic compounds—that is, that the same forces are concerned in the building up of their molecules from the elements—being clearly recognised, no scientific basis for a division was apparent. The division appeared then, as it does now, essentially one of convenience. Probably the main reason why the study of organic chemistry has been held so distinct from that of inorganic chemistry is that the two branches appeal, to a great extent, to different classes of workers in technological fields—inorganic chemistry to those who are concerned with the so-called “heavy chemicals” (alkalis, mineral acids, and salts, and with metallurgy, etc.), and organic chemistry to those dealing with the manufacture of such products as dyes, essences, etc. From this purely utilitarian standpoint there is much to be said for the separation of the two branches.

It is unnecessary to discuss in any detail the various definitions of organic chemistry that succeeded each other after the fall of the “vital force” distinction. The fact that the element carbon is the essential constituent of all organic compounds led very soon to the definition of organic chemistry as “the chemistry of the carbon compounds,” and it was clearly stated in the leading textbooks of the middle of last century that the necessity

<sup>1</sup> Cf. Meldola, *The Chemical Synthesis of Vital Products*, vol. i.; 1904.

<sup>2</sup> Cf. Chapter xiii. p. 352.

of treating organic compounds separately arises from the large number and importance of the carbon compounds and of the necessity of a division of labour in the interest of scientific research, and not from any difference that exists between organic and inorganic compounds "either in their component materials, in the forces which hold these materials together, or in the number and the mode of grouping of their atoms."<sup>1</sup>

Although this is the view held to-day, the definition is somewhat lacking in accuracy, since certain simple carbon compounds, such as carbon dioxide and such derivatives as marble, magnesite, and other carbonates naturally fall in the domain of inorganic or mineral chemistry. Other derivatives of carbonic acid, however, such as urea and carbamic acid, are equally characteristic organic compounds. There is really no line to be drawn here; "it is better felt than defined," as Gmelin said ninety years ago. The necessity for a division lies essentially in the number and in the special characteristics of organic compounds. These latter demand, not only special theoretical considerations, but also special methods of practical manipulation in their study. Compared with the compounds of other elements, those of carbon are characteristically unstable. They are with few exceptions decomposed by high temperatures, such as inorganic compounds are able to withstand without decomposition. It is doubtless this feature which causes one intuitively to class the metallic carbonates amongst the inorganic compounds, although they are so closely allied to certain of the organic compounds. The large number of the carbon compounds and the variety of ways in which the atoms are linked together have necessitated the development of special methods for the actual laboratory work connected with their investigation, and with the help of these it has been possible to obtain a special insight into the structure of organic compounds.

In the case of most inorganic compounds one has to be content to know the nature and relative number of the atoms present; for instance, one substance, and only one, having the composition of potassium permanganate or of phosphoric acid is known. In organic chemistry this does

<sup>1</sup> Kekulé, *Lehrbuch der organischen Chemie*, Vol. I. p. 11; 1851.

not suffice. To use an analogy, suppose a wall be built of red, white and blue bricks, as representing three elements, and that there are nine red, ten white, and three blue bricks. Were these to represent carbon, hydrogen, and oxygen respectively, what the organic chemist has to find out, and is able to find out, is not only the number and nature of the bricks, but also the way in which they are arranged relatively to each other. At present he has discovered examples of eighty-two ways in which these twenty-two bricks can be arranged; he has a number more to find out, but at least he has the means of distinguishing eighty-two different patterns.

Except in so far as the inorganic chemist has been able to adopt something of the methods of organic chemistry—and this adaptation has been as yet very limited—he has in most cases to be satisfied with a knowledge of the number and nature of his bricks; he knows what the wall is made of, but he cannot read its pattern. Inorganic compounds of the same composition, but differing in the relative arrangement of the constituent elements, are scarcely known as yet. New methods of investigation may at any moment place the inorganic chemist on a level with the organic chemist in this respect, but at present he is behindhand.

These indications are sufficient to show the necessity for separating the study of the chemistry of the carbon compounds from that of the other elements. The definition of organic chemistry as “the chemistry of the hydrocarbons and their derivatives” proposed by Schorlemmer appeals to one as exact and fitting in consideration of the importance of the hydrocarbons, which are the mother substances of all organic compounds. But on examination it is no improvement on the previous definition, because all carbon compounds can be derived from the hydrocarbons. Organic chemistry is therefore best and most simply defined as “the chemistry of the carbon compounds.”



## CHAPTER II.

### THE STRUCTURE OF ORGANIC COMPOUNDS.

Carbon and hydrogen the fundamental elements of organic compounds—Empirical and molecular formulae—The Radical theory—The theory of Types—Valency and the Linking of Atoms—Isomerism—The structure of hydrocarbons; the law of the Linking of Atoms.

Of the eighty known elements, three only are concerned in the building up of the majority of the carbon compounds—namely, carbon, hydrogen, and oxygen. Apart from these, nitrogen is the most frequent constituent, and as was long ago observed, phosphorus and sulphur occasionally occur in animal products. In the laboratory it is possible to introduce many of the other elements into organic compounds. Carbon is the characteristic constituent of them all, and its compounds with hydrogen, oxygen, and nitrogen, either separately or conjointly, are more numerous than those of all the other elements put together. The question at once arises, how is it that so many compounds can be built up from so few elements? The main reason is that carbon possesses in an extraordinary degree the capacity of combining with itself. It is accordingly possible to obtain compounds in which a large number of carbon atoms are linked together, either in the form of a chain (which may be either continuous or branched) or of a ring, or of an almost infinite variety of combinations of rings and chains. Thus, compounds are known in which as many as sixty carbon atoms are directly united to each other. Since other atoms are attached to each of the carbon atoms in these chains or rings which form the nuclei of the organic compounds, it is readily seen that an almost infinite multiplicity of compounds may result. As far as is known at present, other elements share this

property of linking with themselves only in a minor degree, and thus their power of forming compounds is much more limited.

*Empirical and Molecular Formulæ.*—To arrive at a knowledge of the elementary composition of any compound is the first step towards ascertaining its chemical nature or constitution. It is first necessary to find out the elements of which it consists and the relative proportions of these elements. Since the number of elements present is almost always restricted to the few mentioned above, standard methods of analysis have been devised which are applicable to the great majority of organic compounds. This forms an instance of the difference in the practical methods which are applied in inorganic and organic chemistry respectively. In the former, a large variety of analytical methods is necessary, according to the elements present and the separations to be effected; in the latter the procedure is almost always identical. From analysis the simplest expression of the ratio of the atoms is arrived at, which is represented by what is known as an *empirical formula*, such as  $\text{CH}_2\text{O}$ . This means that the substance consists of carbon, hydrogen, and oxygen, and that there are two atoms of hydrogen in proportion to every one of carbon and of oxygen present. But such a formula does not necessarily show the actual number of atoms present in the molecule, for the latter may be represented by any simple multiple of the above. Thus the compound may equally well be  $\text{C}_2\text{H}_4\text{O}_2$ ,  $\text{C}_3\text{H}_6\text{O}_3$ ,  $\text{C}_6\text{H}_{12}\text{O}_6$ , etc., and compounds of each of these formulæ are known. A compound which has the empirical formula  $\text{CH}_2\text{O}$  by analysis must have the composition  $(\text{CH}_2\text{O})_n$  where  $n$  is a whole number. The next step is therefore to find which of these formula is the true one. Analytical determinations cannot decide this point, but there are several physical methods by means of which the size of a molecule (the value of  $n$ ) can be ascertained. Formerly this could only be effected with substances which could be boiled without decomposition, by ascertaining the density of their vapour, a method based on Avogadro's hypothesis (1811) that "equal volumes of all gases under the same conditions of temperature and pressure contain an equal number of molecules." This limitation has been removed

as an outcome of the researches of Pfeffer, Raoult, van't Hoff, and Ostwald (1877 to 1887), who have shown that the laws relating to the properties of gases apply also to dissolved substances in dilute solution, or that "solutions of different substances in the same solvent, which contain an equal number of molecules of the dissolved substance in one and the same quantity of the solvent, have the same osmotic pressure, vapour pressure, boiling point and freezing point." The practical application of this relation for the determination of the molecular weights of dissolved substances has been of great service. The commonest laboratory methods consist in the determination of the depression of the freezing point or of the rise in the boiling point of a solvent by the introduction of the compound the molecular weight of which is to be determined. Since the rise of the boiling point or the lowering of the freezing point brought about by a given amount of any dissolved substance is inversely proportional to the molecular weight, it is a simple matter to find the molecular weight of a compound under investigation by comparing its effect with that of a compound of known molecular weight.

These methods are of wide application and yield sufficiently accurate results; a considerable number of solvents, such as acetic acid, ether, alcohol, and phenol, are available, so that it is usually possible to find a suitable solvent for most substances. Water is not applicable in the majority of cases, owing to the dissociation of the dissolved substances which frequently occurs in aqueous solution; also benzene and some other liquids are not reliable because many substances exist in the form of double molecules in these solvents. Further, an obvious precaution is to choose a solvent which has no chemical action upon the substance under investigation. The determinations are readily carried out, and are in common use in modern research.

With the help of these methods the *molecular formula* is ascertained, as distinguished from the empirical formula. Thus, in the above instance it is possible to decide between the formulæ  $\text{CH}_2\text{O}$ ,  $\text{C}_2\text{H}_4\text{O}_2$ ,  $\text{C}_3\text{H}_6\text{O}_3$ , etc., and to find out how many atoms are actually present in the molecule.

✱ *The Theories of "Radicals" and "Types."*—It was stated in the previous chapter that no less than eighty-two

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substances are known, each consisting of nine atoms of carbon, ten of hydrogen, and three of oxygen, and having therefore the empirical formula  $C_9H_{10}O_3$ . This is also their molecular formula. The number and kind of atoms present in each of these compounds is identical. In the early history of organic chemistry it was looked upon as a remarkable phenomenon that more than one compound should have the same elementary composition. After what has been said as to the property of carbon atoms of combining with one another in a great variety of ways, it will not be surprising that compounds should be found which are identical in composition but different in "structure." To use the former analogy, the pattern of the wall may be different, although the bricks used are the same. The chief and most difficult work of the organic chemist is to elucidate this pattern.

Liebig and Wöhler's investigation on "The radical of benzoic acid" led to the first attempts to obtain an insight into what is now termed the *constitution* or *structure of organic compounds*, and soon developed to the *Theory of Radicals*. Oil of bitter almonds (benzaldehyde) was shown to have the formula  $C_7H_6O$ ; on oxidation it forms an acid,  $C_7H_6O_2$ , from which a substance,  $C_7H_5OCl$ , was prepared, which could easily be converted into the original compound, oil of bitter almonds. In these three substances:—

$C_7H_6O$ .	Oil of bitter almonds,
$C_7H_6O_2$ .	Benzoic acid,
$C_7H_5OCl$ .	Benzoyl chloride,

one group of atoms remains unchanged in their passages from one into the other—the group  $C_7H_5O$ , called *Benzoyl*.<sup>1</sup> In oil of bitter almonds it is united to an atom of hydrogen, in benzoic acid to one of hydrogen and one of oxygen, and in the third compound—benzoyl chloride—to one of chlorine, thus:—

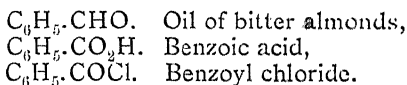
$C_7H_5O.H$ .	Oil of bitter almonds.
$C_7H_5O.OH$ .	Benzoic acid.
$C_7H_5O.Cl$ .	Benzoyl chloride.

This same group was found to be present in many derivatives of all three substances; it was called the

<sup>1</sup> The ending from  $\lambda\eta$ , stuff or matter.

*radical* of benzoic acid, and the term *compound radical* was given to such a group of atoms, which by their remaining unchanged throughout a series of compounds really played the part of elements. Cyanogen, a compound of carbon and nitrogen, discovered by Gay Lussac in 1815,<sup>1</sup> was recognised by Liebig as a characteristic compound radical on account of the many closely related compounds known in which these two elements occur combined, as in cyanogen itself. In Liebig's own words (1838)—“Cyanogen is a radical because it is the never-varying constituent of a series of compounds; because it can be replaced in these by simple bodies; because in its combinations with a simple body the latter can be separated and replaced by equivalents of other simple bodies. Of these three chief characteristics of a compound radical, two at least must be fulfilled ere it can be regarded as a compound radical.”

This definition of Liebig's still holds good, but a knowledge of the radical in a group of allied compounds is not in itself sufficient to establish the constitutional formula of a substance. It was chiefly valuable as the first stepping-stone towards a knowledge of the structure of a molecule. Liebig and his followers regarded it as ample, and their ideas led to an active search for such unvarying atomic groupings in many series of organic compounds, a search which illuminated many dark corners of organic chemistry. It is impossible to over-estimate the stimulus given to research by these ideas, and their value still exists, but they are not sufficiently far-reaching. For instance, to return to the radical *benzoyl*, the characteristic group of atoms in the three compounds referred to above. The same compounds contain another grouping of six carbon and five hydrogen atoms, which is equally characteristic of them all:—



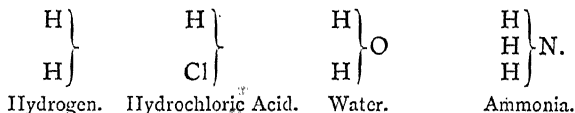
This group or radical  $\text{C}_6\text{H}_5$  is now known as the *Phenyl* group, and just like benzoyl is an unchanging constituent.

<sup>1</sup> *Ann. Chim. Phys.*, 1815, xcv. 136.

of these and many allied compounds. Which then is their true radical, benzoyl or phenyl? It depends upon the reactions or changes considered. In certain chemical reactions the benzoyl group remains intact, in others it is destroyed and the phenyl group remains. In fact the latter is part of the former, and consequently the more permanent throughout a series of changes.

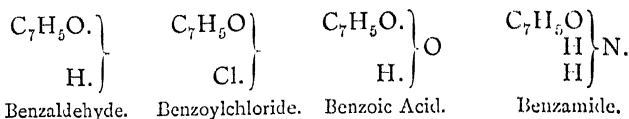
This is sufficient to show that the knowledge of the composition of the radical in a group of compounds enables the chemist to obtain an insight into their relationship, but it does not go beyond this. The same radicals were found to occur in compounds of entirely different chemical character; these were brought under a common head by the radical theory, but the relationships of compounds of similar chemical character remained masked until Dumas' *Theory of Types* (1839)—which was especially developed by Gerhardt (1853)—had received the support of the experimental investigations of Hofmann, Williamson, and Wurtz. This was the second great step towards understanding the constitution of organic compounds. The type theory followed as a consequence of the discovery by Dumas<sup>1</sup> that the hydrogen atoms in acetic acid could be successively replaced by chlorine atoms giving rise to compounds very similar to acetic acid in their general properties. The character of organic compounds thus appeared to depend rather upon the arrangement of their constituent atoms than upon the actual radicals present.

According to the type theory, the structure of all organic compounds was compared with that of certain simple, typical inorganic substances. In the start four simple types were selected: hydrogen, hydrochloric acid, water, and ammonia:—

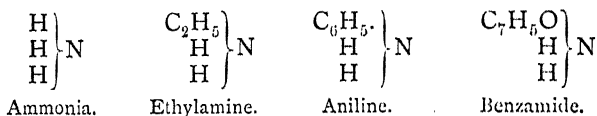


The benzoyl compounds built up on these types would be arranged thus:—

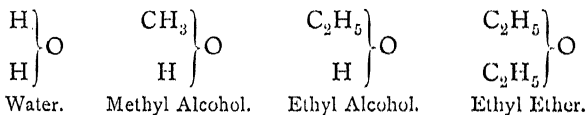
<sup>1</sup> *Annalen*, 1839, xxxii. 101.



These relationships are in themselves no extension of those indicated by the radical theory. Their chief value lies in the fact that they bring compounds which are similar in chemical character under the same heading. Thus, the analogy of benzamide, built up on the ammonia type, with aniline, ethylamine, and the other organic ammonias discovered by Hofmann and Wurtz became apparent.



Similarly, Williamson, in 1850, showed that the alcohols and their ethers could be referred to the *water type*. In the former one, in the latter two atoms of hydrogen are replaced by the organic radicals:—



Corresponding relationships amongst many other groups of compounds, built up on the several types, became evident, and lent valuable aid not only in understanding these analogies, but also in pointing the way successfully for the preparation of new compounds. Other and more complex types were added, and for quite ten years (1848 to 1858) the theory of types in combination with the radical theory was the basis for all investigations.

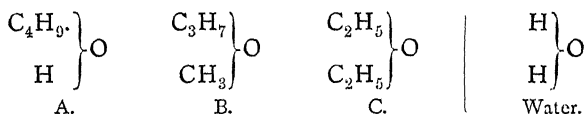
This combination was largely due to Gerhardt, who in addition gave a modified interpretation to the term "radical," one which soon supplanted the old view, and remains still in use. Radicals, according to Gerhardt, are the groups of atoms which remain unchanged throughout a series of reactions, which fulfil indeed the actual condi-

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tions laid down by Liebig, but which *cannot be isolated*, as Liebig had supposed. This last is the new condition. Free cyanogen, which was Liebig's radical, is  $(\text{CN})_2$ . CN is Gerhardt's radical as in HCN (hydrocyanic acid), it cannot exist free; when its isolation is attempted the molecule  $(\text{CN})_2$  results.

*Valency and the Linking of Atoms.*—The object of the above theories, as well as of the experimental investigations to which they gave rise, was to obtain an insight into the manner in which the elements of organic compounds are grouped or arranged, but problems soon arose for which they did not suffice. An example will best show their value and their limits.

Seven compounds are known having the formula  $\text{C}_4\text{H}_{10}\text{O}$ . Four of these contain a radical  $\text{C}_4\text{H}_9$ ; two of them a radical  $\text{C}_3\text{H}_7$ , and a second radical  $\text{CH}_3$ ; the seventh compound contains the radical  $\text{C}_2\text{H}_5$ —but it is present in the molecule twice. All these substances are built up on the "water type," and may be represented as follows:—



In A only one atom of hydrogen in the water type is replaced by a radical, in B and C both hydrogen atoms are replaced. Thus, the radical and type theories suffice to show the distinction between the compounds A, B, and C—that is, between three of the seven—but they give no clue to any reason for the existence of four compounds on the type of A, or of two on that of B.

Compounds having the same molecular composition are called *isomers*,<sup>1</sup> and the phenomenon is known as *isomerism*. It is evident that the theory of types in conjunction with the radical-theory can explain certain isomeric relations, but it is equally evident that it cannot account for others. The above example shows that there may be, not only isomeric compounds containing different radicals, but also isomeric radicals. In order to gain a thorough insight into the structure of the molecule it is necessary to carry

<sup>1</sup> From *isos*, equal; and *μέρος*, a share or portion.



the inquiry to the ultimate particles of which radicals are composed—that is, to ascertain the arrangement of the atoms in these radicals, and not to be satisfied with conclusions only as to the various groups of atoms present.

This was first clearly recognised by Kekulé in a very remarkable theoretical paper which may be fitly regarded as the foundation of the present theories of organic chemistry. The title of the paper, which was published in 1858, is “On the Constitution and Metamorphoses of Chemical Compounds and on the chemical nature of Carbon.”<sup>1</sup> Kekulé says—“I regard it as necessary, and in the present state of chemical knowledge as in many cases possible, to explain the properties of chemical compounds by going back to the elements themselves which compose these compounds. I no longer regard it as the chief problem of the time to prove the presence of atomic groups which, on the strength of certain properties, may be regarded as radicals, and in this way to refer compounds to a few types which can hardly have any significance beyond that of mere pattern formulæ. On the contrary, I hold that we must extend our investigation to the constitution of the radicals themselves; that we must ascertain the relation of the radicals to one another, and from the nature of the elements deduce both the nature of the radicals and that of their compounds.”

This new possibility is founded upon Kekulé's view of the *valency* of the elements and on the mutual linking of carbon atoms, a view which was independently arrived at by Couper.<sup>2</sup> Frankland had six years previously (1852) introduced the conception of valency into chemistry, and based his typical formulæ essentially on the valency of the elements; but it was Kekulé who founded the theory of the chemical structure of organic compounds upon this doctrine.<sup>3</sup>

The number of atoms with which any element can combine is a characteristic property of the element. This

<sup>1</sup> “Ueber die Constitution u. Metamorphosen der chemischen Verbindungen u. ueber die chemische Natur des Kohlenstoffs.” *Annalen*, 1858, cvi. 129.

<sup>2</sup> *Comptes rend.*, 1858, xlv. 1257.

<sup>3</sup> Cf. F. R. Japp, “Kekulé Memorial Lecture” (*J. Chem. Soc.*, 1898; lxxiii. 97), in which the historical development of this subject is fully treated.

*combining power* or *valency* is different for the different elements, and is referred to some standard as unity. In the simplest hydrocarbon,  $\text{CH}_4$ , called "marsh gas" or "methane," four hydrogen atoms are attached to one carbon atom; accordingly the carbon atom has four affinities, each of which is satisfied by the combination with one hydrogen atom. Each hydrogen atom is thus seen to possess only one such affinity. Hydrogen forms a compound, and only one, with chlorine—namely, hydrogen chloride, or hydrochloric acid,  $\text{HCl}$ . Hence, it appears that chlorine, like hydrogen, possesses only one affinity. Such elements are regarded as having unit valency and are called *univalent*. As is to be expected from the above, it is found that carbon forms a compound,  $\text{CCl}_4$ , with chlorine; *i.e.*, each of the four *valencies* of the carbon atom is united to a univalent chlorine atom. Similarly, one atom of oxygen combines with two of hydrogen, and oxygen is therefore concluded to be *divalent*; nitrogen is *tervalent*, and carbon *quadrivalent*. These relations are expressed in the formulæ:—

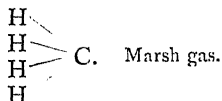
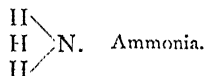
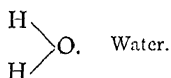
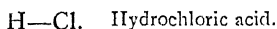
$\text{HCl}$	$\text{H}_2\text{O}$	$\text{H}_3\text{N}$	$\text{H}_4\text{C}$
Hydrogen chloride.	Water.	Ammonia.	Marsh gas.

Kekulé clearly recognised this quadrivalency of carbon, as is shown by the following extract from the above-mentioned paper:—"If we consider the simplest compounds of this element,  $\text{CH}_4$ ,  $\text{CH}_3\text{Cl}$ ,  $\text{CCl}_4$ ,  $\text{CHCl}_3$ ,  $\text{COCl}_2$ ,  $\text{CO}_2$ ,  $\text{CS}_2$ , and  $\text{CNH}$ , it is striking that the quantity of carbon which chemists consider as the smallest possible, the atom, always combines with four atoms of a monatomic (univalent) element, or two of a diatomic (divalent) element, so that in general the sum of the chemical units of the elements combined with carbon is equal to four."

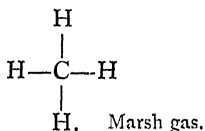
The theory of valency is concerned only with the number of affinities which an atom possesses, and not with the force with which the atoms are united.

The value of the theory is at once evident. Since carbon exerts four affinities, oxygen two, and hydrogen one, a most useful basis is available for the elucidation of the structure of organic compounds. With many elements the valency varies in its different compounds. Nitrogen, for instance, is not always trivalent; in fact,

it appears to be capable of varying its combining power from one to five, in terms of the unit. The valency of carbon, on the other hand, is practically constant. It is true that the simplest oxide of carbon, carbon monoxide, CO, appears to contain a divalent carbon atom, and carbon is also probably divalent in hydrocyanic acid, the isonitriles, and in a few other compounds, but with these exceptions the quadrivalency of carbon may be regarded as firmly established. It means, as far as the building up of compounds is concerned, that every carbon atom has the power of combining with four atoms of a univalent element such as hydrogen. It is usual to speak of these atoms as being *linked* together, though the term *linking* is somewhat inaccurate as applied to inter-atomic forces, and to give a representation of such linkings by means of formulæ in which the symbols of the atoms are united by lines, a method first suggested by Couper (1854), *e.g.* :—



These lines are in no way intended to represent the direction of the linkings; they are simply and solely to express the number of affinities of the atoms. The symmetry of marsh gas is, in fact, better shown by grouping the four hydrogen atoms round the carbon atom thus :—

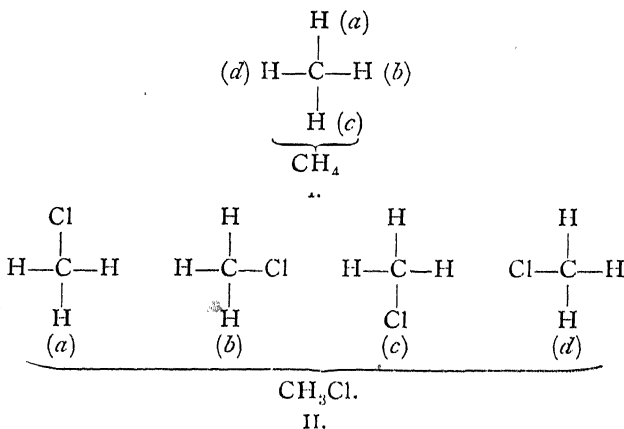


Or, as will be shown later (Chapter XII.), still better by considering the carbon atom as a point in space and supposing the affinities to be directed uniformly in

three dimensions. Such diagrammatic formulæ as the above are called *graphic formulæ*.

Marsh gas is the simplest hydrocarbon that can exist; by studying the manner in which other hydrocarbons can be derived from it a good idea is obtained of the possible conditions of combination of carbon and hydrogen.

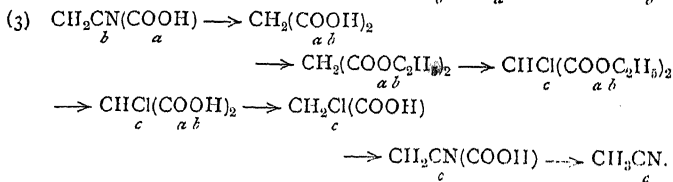
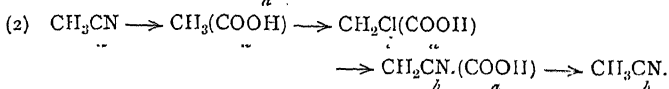
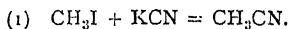
*The Structure of Hydrocarbons.*—Before considering the manner in which the combining power of carbon is concerned in the building up of its compounds, it is necessary to look closely into the nature of its simplest compound with hydrogen, so as to grasp the full meaning of the above method of representation. The most important consideration is whether these four linkings, each of which represents a part of the combining power of carbon, are all equivalent. Is it immaterial which of the four is in combination with any univalent atom? This can only be answered by the safe test of direct experiment. Suppose one atom of hydrogen in marsh gas be replaced by an atom of chlorine, which from its combination with hydrogen in hydrochloric acid is known to be univalent, is the resulting compound, which will have the formula  $\text{CH}_3\text{Cl}$ , always the same, whichever atom of hydrogen is replaced? Representing the hydrocarbon by the graphic formula used above, any one of the four hydrogen atoms *a*, *b*, *c*, or *d* might be replaced by chlorine thus:—



The four compounds (II.) would be different if the four bonds of the carbon atoms were dissimilar; if one of the four differed from the remaining three, then there would be two isomers. Despite the numerous laboratory methods available for the preparation of the compound  $\text{CH}_3\text{Cl}$  (methyl chloride) and other analogous mono-substitution products of methane, no instances of dissimilarity amongst such products have ever been observed; in all cases one and the same substance is obtained. In addition, Henry<sup>1</sup> has adduced direct experimental evidence to show that the formulæ *a*, *b*, *c*, and *d* (II.) for a mono-substitution product of methane are identical. This he effected as follows:—A compound was first prepared with its substituent, say, at *a*; a second substituent was then introduced, the first eliminated, and this new substituent replaced by the same substituting group as that originally introduced at *a*. This second substituent must obviously occupy a different position in the molecule, say *b*. Again starting from a compound in which two substituents were already present in the positions *a* and *b*, a third compound was prepared by replacing a third hydrogen atom, and then eliminating the substituents at *a* and *b*; in a similar manner the fourth hydrogen atom was replaced by the same substituent as that originally introduced, the position of which was therefore at *c* and *d* respectively in the two latter compounds.<sup>2</sup>

<sup>1</sup> *Comptes rend.*, 1887, cii. 1106; and *Bull. Acad. roy. Belgique, Classe des Sciences*, 1906, 722; *Chem. Centr.*, 1907, i. 1312.

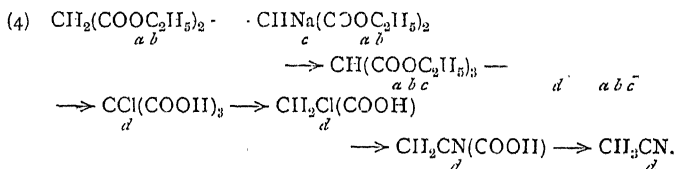
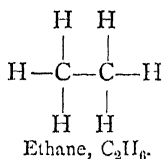
<sup>2</sup> The following scheme represents, in outline, the reactions which were chosen to obtain the four methyl cyanides containing the CN group in the positions *a*, *b*, *c*, and *d* respectively:—



## STRUCTURE OF ORGANIC COMPOUNDS.

The four products thus obtained were absolutely identical in all their physical properties (boiling point, specific gravity, etc.), thus proving the equivalence of the four valencies of the carbon atom. This proof is open to the objection that a change in the position of the substituents, a molecular rearrangement, might occur during the reactions involved, but in view of the nature of the reactions, this is improbable.<sup>1</sup> From the equivalence of the four affinities of the quadrivalent carbon atom, it is possible to show how the atoms of carbon and hydrogen may be disposed in any carbon compound of which the composition is known.

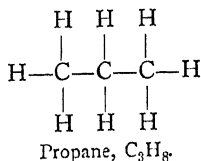
A compound closely related to marsh gas is ethane, which has the formula  $C_2H_6$ . This formula tells nothing, however, of the way in which the atoms are linked together. It is evident that since carbon is the only one of the two elements which has more than one linking power or valency, the atoms in the molecule of ethane must be held together by the direct union of the two carbon atoms. If the carbon atoms be linked together by a single bond, each of the atoms will have three remaining affinities, which are available for the combination of the hydrogen atoms. These six affinities exactly suffice for the number of the hydrogen atoms in ethane, and the only possible formula for this compound is therefore:—



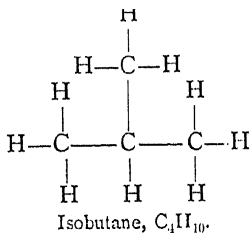
A similar series of reactions was carried out, in which the four nitromethanes were prepared.

<sup>1</sup> Nef (*J. Amer. Chem. Soc.*, 1908, xxx. 645) is of opinion that intramolecular changes are likely to take place in such reactions.

Proceeding to the next higher hydrocarbon, propane,  $C_3H_8$ , there are three carbon atoms which must be united together as shown below. One of the carbon atoms must use up two of its affinities in linking up with the other carbon atoms, and each of the others must use up one of its affinities in the same way. This leaves eight affinities for the hydrogen atoms.



The structure of these hydrocarbons is thus arrived at; that is, a knowledge of the manner in which the atoms forming the molecule are mutually disposed. The method of combination is very simple in these instances, but when more than three carbon atoms are united together the conditions become more complex, although dependent upon the same fundamental factors, which have led to what is known as the *Law of the Linking of Atoms*. The reason for the greater complexity of the molecules is that the conditions of combination are no longer restricted to simple chains of carbon atoms, but may give rise to branched chains, as for instance:—

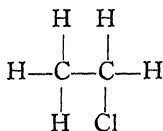


Two hydrocarbons of the formula  $C_4H_{10}$  exist, three of the formula  $C_5H_{12}$ , and the number increases step by step. No less than 802 formulæ are theoretically possible for a hydrocarbon  $C_{13}H_{28}$ . This will be rendered clearer by the following considerations.

Methane,  $CH_4$ , is a symmetrical molecule; it is im-

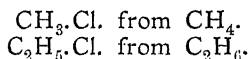
## STRUCTURE OF ORGANIC COMPOUNDS.

material which of the hydrogen atoms is replaced by an atom of chlorine, as already shown. Ethane,  $C_2H_6$ , the next simplest hydrocarbon, is also symmetrically built up, and only one modification of a compound derived from it by replacing an atom of hydrogen by one of chlorine is possible. The formula of this compound,  $C_2H_5Cl$  (ethyl chloride), is represented graphically thus:—

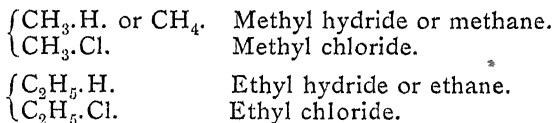


Ethyl chloride.

The relation of these two chlorine compounds to the hydrocarbons from which they are derived is shown in the formulæ:—



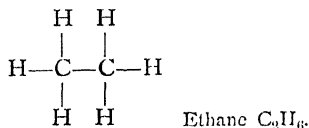
$CH_3Cl$  may be regarded as methane in which a hydrogen atom has been replaced by chlorine; it contains a radical,  $CH_3$ , united to the univalent chlorine atom. Similarly, the group  $C_2H_5$ , is united to chlorine in the corresponding derivative of ethane; these groups, which are the radicals derived from the two hydrocarbons, are called *methyl* and *ethyl* respectively. They cannot exist in the free state because they both contain one of the carbon affinities or linkings unsaturated; their compounds arise when this last linking is satisfied. In the hydrocarbons themselves it is satisfied by a hydrogen atom; these, therefore, may be regarded as the hydrides of the radicals and the chlorine substitution products as the chlorides, analogous to an inorganic chloride such as  $KCl$ , chloride of potassium, or to hydrochloric acid (chloride of hydrogen)  $HCl$ , thus:—



A hydrogen atom cannot exist free; when liberated from its compounds it combines with another atom to form a



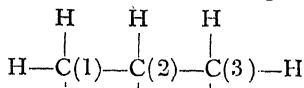
molecule; hydrogen is univalent, and  $\text{H—H}$  represents  $\text{H}_2$  or the free hydrogen molecule. Nor can the radicals methyl and ethyl exist alone, but similarly to hydrogen they unite with themselves to form stable molecules. When a methyl group, liberated from one of its compounds, unites with a second similar group the molecule formed must evidently be built up thus:—



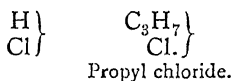
This is ethane. As a combination of two methyl radicals it appears as “Dimethyl,” which is a perfectly accurate nomenclature. At one time ethyl hydride and dimethyl were regarded as different compounds, viz.:— $\text{C}_2\text{H}_5\cdot\text{H}$ , *ethyl hydride*;  $\text{CH}_3\cdot\text{CH}_3$ , *dimethyl*. The radical and type theories seemed to point to a difference here, but the laws of atomic linking dispelled the idea, and Schorlemmer (1865) proved the identity of the two by showing that the compound obtained by replacing one atom of hydrogen by one of chlorine was absolutely identical in both cases, one and the same ethyl chloride,  $\text{C}_2\text{H}_5\text{Cl}$ .

It is further possible to unite the radicals methyl and ethyl to form a compound; the formula  $\text{CH}_3\text{—C}_2\text{H}_5$  or  $\text{C}_3\text{H}_8$  will represent the combination. This is *propane*, the structural formula of which was given above. When two ethyl radicals are joined the compound formed will be  $\text{C}_2\text{H}_5\text{—C}_2\text{H}_5$  or  $\text{C}_4\text{H}_{10}$ . This hydrocarbon is called *butane*.

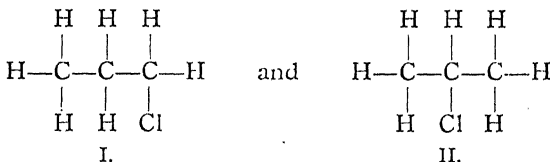
Propane,  $\text{C}_3\text{H}_8$ , is clearly ethane in which a hydrogen atom is replaced by a methyl group or radical; it is methyl-ethyl. There is obviously only one way in which the methyl group can replace an atom of hydrogen, just as there is only one ethyl chloride possible. The linkings of the carbon atoms must therefore be disposed as follows:—



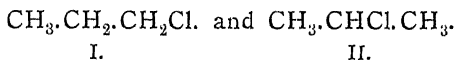
This grouping of the atoms differs, however, in one important detail from that in ethane or methane. The hydrogen atoms are no longer symmetrically arranged. Of the three carbon atoms two (1 and 3) are similar, each being united to three atoms of hydrogen and one of carbon; but the third carbon atom (2) has its affinities differently disposed, two only are linked to hydrogen and the remaining two to two atoms of carbon (1 and 3). If one hydrogen atom in a compound of this structure be replaced by chlorine or any other univalent atom or group, the resulting product must evidently be different according as it is one of the three hydrogen atoms attached to either of the carbon atoms 1 or 3, or one of the two hydrogen atoms attached to the carbon atom 2 that is substituted. The radical of propane is  $C_3H_7$ , *Propyl*, and  $C_3H_7.Cl$ , *Propyl chloride*, is the analogue of ethyl chloride. The theory of types would represent this compound on the hydrochloric acid type thus:—



But there are two propyl chlorides. The above formula for propane at once accounts for them:—



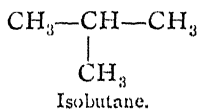
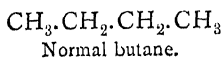
It is unnecessary to write such formulæ fully; the differences are equally intelligible in the following form:—



I. is called *Normal propyl chloride*, and II. *Isopropyl chloride*.

The *isopropyl* group forms a radical, just as does the *normal propyl* group. Whenever the radical propyl forms part of a compound two isomers are possible on these lines,

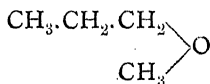
and in most instances both are known. This experimental support thus given to the law of the linking of atoms is repeated again and again amongst organic compounds. Butane,  $C_4H_{10}$ , is the hydrocarbon resulting from the union of two ethyl radicals; two hydrocarbons of this formula are known. The two ethyl radicals when written thus  $CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3$  show that butane is propane in which a hydrogen atom is replaced by methyl. But a methyl group can take either of the above positions in the propane molecule; the two butanes are thus accounted for:—



The second compound, isobutane, appears as methane in which three hydrogen atoms have been replaced by three methyl groups; it may be correctly called *Trimethyl-methane*.

The isomerism of the seven compounds of the formula  $C_4H_{10}O$  previously referred to (page 19) can now be accounted for.

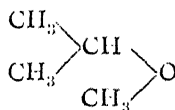
The difference in the two compounds  $\begin{array}{c} CH_3 \\ C_3H_7 \end{array} \rangle O$  evidently consists in the one containing the radical propyl, the other isopropyl, and their constitutional formulæ will be:—



I.

Methyl-propyl ether.

and



II.

Methyl-isopropyl ether.

The existence of four compounds of the type  $\begin{array}{c} C_4H^r \\ 1. \end{array} \rangle O$  can be similarly explained on the basis of the law of the linking of atoms.

The study of this more refined isomerism of organic compounds is sufficient to show how important and helpful

the law of the linking of atoms has been. Not only did it serve to explain isomeric relationships previously incomprehensible; it also pointed out new possibilities, many of which have been subsequently realised.

It remains to inquire what means there are for arriving at a knowledge of the constitutional formulæ of compounds—that is, of ascertaining the manner in which the atoms of their molecules are grouped together. Isomeric substances are distinguished by their physical properties, such as melting point, boiling point, crystalline form, and solubility. Their constitutional or structural formulæ are arrived at by a study of their methods of formation, of the changes they undergo, and of the products that result by their decomposition. Such formulæ express in a concise form the chemical nature of the compound, and, moreover, indicate its typical properties.

There is still a further condition of isomerism, the most recent and perhaps the most interesting—that due to a difference in the spatial arrangement of the atoms. Pasteur in 1848 and J. Wislicenus in 1869 were the first to show that two different substances could be apparently identical in respect to their chemical structure; many other instances have followed, typically that of two closely-related acids—maleïc and fumaric. Such substances are now recognised as *geometrical* or *stereochemical isomers*. Their existence has in no way diminished the value of the law of the linking of atoms for structural chemistry, but it has necessitated an extension of two-dimensional formulæ to three dimensions. New conditions and possibilities then arise, which will be considered in Chapter XII. Conversely, instances are now known in which two isomeric compounds pass so easily into one another that the same substance appears from its reactions to have two different formulæ. This gives rise to the phenomenon of tautomerism, which will be dealt with in Chapter XIV.

## CHAPTER III.

### THE CLASSIFICATION OF ORGANIC COMPOUNDS.

Homologous series of hydrocarbons and of their derivatives—The value of homology in the study of organic compounds—Aliphatic or open-chain compounds—Saturated and unsaturated aliphatic compounds—Cyclic or closed-chain compounds—Isocyclic and heterocyclic compounds.

*Homologous Series of Hydrocarbons and of their Derivatives.*  
—It was seen in the previous chapter that ethane,  $C_2H_6$ , is derived from methane by the replacement of a hydrogen atom by the methyl group  $CH_3$ . The replacement of a hydrogen atom in ethane by  $CH_3$  gives rise to propane  $C_3H_8$ , and a repetition of this process yields butane  $C_4H_{10}$ . By repeating this substitution of H by  $CH_3$  in this way a series of compounds is obtained containing a chain of carbon atoms, the remaining affinities of which are attached to hydrogen atoms. Each member of the series differs from the preceding member by one atom of carbon and two atoms of hydrogen.

		Difference in composition.
<i>Methane,</i>	$CH_4$	} $CH_2$
<i>Ethane,</i>	$C_2H_6$	
		} $CH_2$
<i>Propane,</i>	$C_3H_8$	
		} $CH_2$ .
<i>Butane,</i>	$C_4H_{10}$	

The compounds are clearly closely related to one another, and it will be shown later that they show a regular gradation in their boiling points and other physical properties as also in their chemical character. The study

of organic chemistry is greatly simplified and systematised by dealing with all the compounds of such a series together. Thus, general methods are available for the preparation and investigation of all the members of a series, and the gradation in physical properties facilitates the study of such groups. The members of each group undergo similar changes with chemical reagents, and in the form of their corresponding radicals (methyl, ethyl, etc.) can be introduced, by similar means, into other molecules.

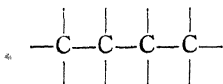
Kekulé recognised this relationship between the allied compounds, and gave the general formula  $C_nH_{2n+2}$  to the group. Since  $n$  carbon atoms have  $4n$  valencies, and  $2n-2$  are required, according to the law of the linking of atoms, for the mutual linking of the carbon atoms, therefore  $4n-(2n-2)$  remain for the hydrogen, or  $2n+2$ . Such a series is known as an *Homologous Series*.

Series in which the members are similarly related exist amongst all the derivatives of the hydrocarbons, such as the chlorides, alcohols, acids, etc.; e.g.:—

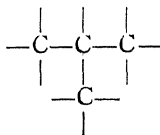
Methyl chloride,	$CH_3.Cl$ .	Methyl alcohol,	$CH_3.OH$ .
Ethyl chloride,	$C_2H_5.Cl$ .	Ethyl alcohol,	$C_2H_5.OH$ .
Propyl chloride,	$C_3H_7.Cl$ .	Propyl alcohol,	$C_3H_7.OH$ .

In each of these groups there is the same constant difference of  $CH_2$  in the composition of the successive members, and similarities in methods of preparation and properties are again characteristic. The value of homology for the classification of organic compounds was first grasped by Schiel (1842), and it has been of very great service in the study of organic chemistry. The marked analogies in homologous groups render the consideration of all the individual members unnecessary; any one member can be studied as typical of the whole group, and the knowledge thus obtained can be applied to the others. A further useful relationship appears amongst the corresponding derivatives of the hydrocarbons. Ethyl alcohol and ethyl chloride are derived from their hydrocarbon ethane, just as methyl alcohol and methyl chloride are derived from methane; homology therefore includes the mutual relationship of the hydrocarbons to all their derivatives.

*Aliphatic or Open-chain Compounds.*—It was seen that in proceeding from methane to ethane, propane, etc., a chain of carbon atoms is gradually built up, and that this chain may be either straight and continuous or branched, as in the case of the two butanes:—



In Butane.



In Isobutane.

There is another large class of compounds in which the carbon atoms are united in the form of a ring, and this ring-structure modifies their properties to such an extent that it is necessary to sub-divide organic compounds into two main classes called the open-chain compounds and the closed-chain or ring compounds respectively. The former are known as the “fatty” or “*aliphatic*” compounds (from *αλοιφής*, fat) since they include the naturally occurring fats and derived compounds.

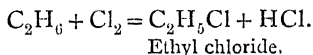
*Saturated and Unsaturated Aliphatic Compounds.*—The hydrocarbons of the methane group are *saturated* compounds. The appropriateness of this term lies in the fact that with the exception of the valencies which are necessary to unite the carbon atoms of the molecule, their affinities are fully saturated with hydrogen atoms. Each hydrocarbon contains, therefore, the maximum number of hydrogen atoms possible; this is expressed by the general formula  $C_n H_{2n+2}$ .

Other open-chain hydrocarbons are known which are poorer in hydrogen. In these the available affinities are not all attached to hydrogen atoms, as in the hydrocarbons considered above. The manner in which the remainder are accounted for will be shown presently. Such compounds are said to be *unsaturated*.

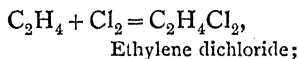
Ethylene,  $C_2H_4$ , and acetylene,  $C_2H_2$ , are the initial members of two homologous series of such hydrocarbons, having the general formulæ  $C_n H_{2n}$  and  $C_{2n} H_{2n-2}$  respectively.

When ethane is acted upon by chlorine, an atom of hydrogen is replaced by one of chlorine, hydrochloric acid

being simultaneously formed. The resulting product, ethyl chloride, is derived from the hydrocarbon by the substitution of chlorine for hydrogen:—



Such *substitution products* are characteristic of all saturated hydrocarbons. The unsaturated hydrocarbons, on the other hand, under analogous conditions, form *addition products*; ethylene and chlorine, for instance, combine directly, without mutual exchange, to form a saturated compound, ethylene dichloride:—



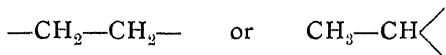
which may also be regarded as ethane with two hydrogen atoms replaced or substituted by their equivalent of chlorine.

Acetylene,  $\text{C}_2\text{H}_2$ , is still poorer in hydrogen; it is a *doubly unsaturated hydrocarbon*. Four additional atoms of hydrogen or of chlorine are necessary to completely satisfy the affinities of the two carbon atoms present. Under suitable conditions it can be converted, first into a compound of the ethylene group, and then into a saturated compound, thus:—



This relation of the three hydrocarbons is typical of their homologues and derivatives.

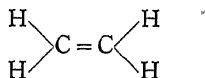
The question naturally arises, how can the law of the linking of atoms account for the existence of hydrocarbons, which contain fewer hydrogen atoms than are required to satisfy the valencies of the carbon atoms present? There are two possibilities, without the admission of a variable valency in carbon; either certain valencies of the carbon atoms remain free and uncombined, or they mutually satisfy each other. The former idea would be expressed, in the case of ethylene,  $\text{C}_2\text{H}_4$ , by such formulæ as:—



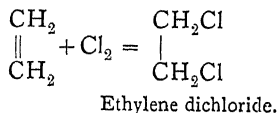


These formulæ are extremely improbable, though recently many investigators are inclined to the opinion that free valencies are not impossible. If free carbon affinities were capable of existence in these hydrocarbons, there is no reason why compounds containing one, three, or five free valencies should not be capable of isolation. Many attempts have been made to prepare such compounds, but no case has been proved with certainty in which an odd number of valencies exists, although a compound, *triphenylmethyl*,<sup>1</sup> which behaves as if it contains a free valency, has been recently prepared. Compounds of this character would become saturated by the addition of an odd number of hydrogen atoms, or their equivalent, but with the above possible exception, all unsaturated hydrocarbons take up an even number of univalent atoms in passing to saturated compounds. Further, as has already been stated, when the radical methyl  $\text{CH}_3$ , which has one such free valency, is liberated from a compound it never separates as such, but unites at the moment of its separation with a second similar radical to form  $\text{CH}_3\text{—CH}_3$  (ethane) by mutual saturation.

The second possibility, that the two carbon atoms in ethylene, for example, account for four instead of two of the carbon valencies is expressed by the formula:—



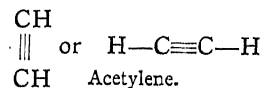
This representation accords well with the chemical behaviour of ethylene. That the addition compound with chlorine is formed by the saturation of the double bond is shown by the fact that the resulting saturated compound is symmetrical:—



A hydrocarbon containing only one carbon atom,  $\text{CH}_2$ , cannot exist according to this view; such a group, when

<sup>1</sup> Gomberg, *Berichte*, 1900, xxxiii. 3150; Cf. Chap. xv. p. 423.

isolated, must at least combine with a second similar group, and  $\text{CH}_2 + \text{CH}_2 = \text{C}_2\text{H}_4$ , or ethylene is what actually results under the experimental conditions that might be expected to give rise to  $\text{CH}_2$ . This is analogous to the combination of two methyl groups to form ethane. In all unsaturated compounds, each unsaturated carbon atom is directly connected with a second carbon atom in a similar condition of unsaturation. These facts are sufficient to show that directly united carbon atoms are responsible for this special structure of unsaturated compounds, which is indicated by a double link in compounds of the ethylene group, and by a triple link in acetylene and its homologues.



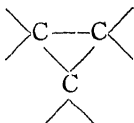
Such formulæ, in addition to representing the manner in which unsaturated compounds take up one or two molecules of elements or their equivalents to form saturated compounds, are also in accord with the requirements of the law of the linking of atoms, in respect to the isomeric relations of the higher members of the groups and of their derivatives.

An apparently weak point in this theory is that one would expect a double bond to unite the carbon atoms more firmly than a single bond, whereas it is found that the double bond is always the weak spot in the molecule, and is very readily attacked by chemical reagents. It will be shown later (Chap. XII.) that such multiple linkings are necessarily in a state of strain, and that the greater stability of a single linking is quite in accord with the most rational views of the nature of valency.

*Cyclic or Closed-chain Compounds.*—In both the saturated and unsaturated hydrocarbons of the aliphatic group, each carbon atom is directly united to the one that precedes or follows it in the chain, or to both.

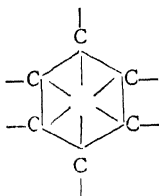
But it is also possible for carbon atoms to be united so as to form a closed chain or ring, or more correctly speaking, a polygon. Such a method of combination

necessitates at least three carbon atoms, linked together as follows:—



Trimethylene ring.

unless ethylene be regarded as a ring composed of two carbon atoms. The most important of these ring or *Cyclic* compounds are those in which six carbon atoms are united together:—



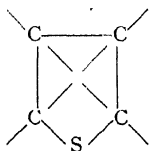
Benzene ring.

This ring or closed-chain combination is found in benzene and its derivatives, a most important group of compounds which includes the aniline colours and many other technically important products. Before the nature of this group was understood, the name of *Aromatic Compounds* was applied to certain naturally occurring products which have since been proved to be benzene derivatives. These compounds possessed a characteristic aromatic odour, and the term has been retained for the group.

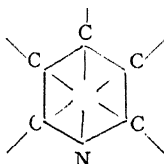
*Isocyclic and Heterocyclic Compounds.*—An important division arises amongst closed-chain compounds. Cyclic compounds are known in which one or more atoms of carbon are replaced by other elements, especially nitrogen, sulphur, or oxygen. The derivatives of some of these are of considerable theoretical and technical importance; the ring compounds containing nitrogen are closely related to the natural alkaloids.

Cyclic compounds, such as benzene, which consist of atoms of the same kind, typically carbon atoms, are called *isocyclic*, those in which other atoms are present *heterocyclic*.

The following are examples of the atomic groupings in the latter:—



Thiophene ring.



Pyridine ring.

Cyclic compounds show certain common characteristics in their methods of preparation, properties, and isomeric relations, all of which stand in marked contrast to those of the aliphatic group.

To summarise, organic compounds can be grouped in three main divisions as follows:—

- I. ALIPHATIC COMPOUNDS.—All open-chain compounds, both saturated and unsaturated—viz., the methane, ethylene, acetylene, etc., hydrocarbons and their derivatives.
- II. ISOCYCLIC COMPOUNDS.—All compounds containing closed chains of only carbon atoms—viz., the benzene or aromatic hydrocarbons, polymethylene hydrocarbons, naphthalene, anthracene, etc., and their derivatives.
- III. HETEROCYCLIC COMPOUNDS.—All compounds containing closed chains having other atoms in addition to carbon atoms—viz., thiophene, pyridine, quino-line, etc., and their derivatives.

This classification, which rests on a sound basis both from a theoretical and experimental point of view, is a valuable aid in the study of the three divisions. There are, in point of fact, certain closed-chain compounds included in the aliphatic division, but the closed chains they contain are due to the presence of certain substituting groups, and are not a characteristic of the grouping of the contained carbon atoms; in their chemical nature they are distinctly aliphatic compounds.

Naturally, this division applies only to compounds of known constitution. There is another large group left—

namely, that of the compounds of unknown constitution. This includes chiefly natural products such as many of the alkaloids, glucosides, proteins, ptomaines, and the like, which have as yet no well-defined place in the system of organic chemistry, but which, although extremely complex, are undoubtedly built up in accordance with the same laws of the linking of the atoms as the compounds, the structure of which is known.

## CHAPTER IV.

### THE ALIPHATIC HYDROCARBONS.

*The Paraffin Series of Hydrocarbons.*—Substitution products.—

Synthetical methods of preparation—Physical properties.

*The Ethylene Series of Hydrocarbons.*—Their chemical character—Formation of addition products.

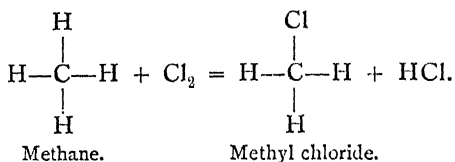
*The Acetylene Series of Hydrocarbons.*—Synthesis of acetylene—Metallic derivatives of acetylene—The metallic carbides and their preparation in the electric furnace.

Further considerations regarding the structure of unsaturated compounds—The Thermochemical relations of saturated and unsaturated hydrocarbons.

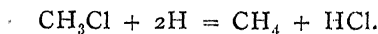
*The Paraffin Series of Hydrocarbons.*—The saturated aliphatic hydrocarbons, typified by methane and ethane, are known as the *Marsh Gas* or *Paraffin* group. The former term is derived from the usual name of the initial member, methane; the latter from *parum affinis*, on account of their inertness towards chemical reagents, first observed with the higher members of the series which constitute ordinary paraffin wax. This stability is the most marked characteristic of the group. Powerful reagents, such as strong nitric or sulphuric acid, are without action on the paraffin hydrocarbons at the ordinary temperature, and even on heating any chemical action is, with few exceptions, very slow. Chlorine, bromine, and fluorine are almost the only substances that re-act at the ordinary temperature. Chlorine forms substitution products, and the hydrogen atoms in the simpler hydrocarbons can be successively and completely replaced by this element. From methane, for instance, the chlorine substitution products are :—

$\text{CH}_4$ .	Methane, or marsh gas.
$\text{CH}_3\text{Cl}$ .	Monochlormethane, or methyl chloride.
$\text{CH}_2\text{Cl}_2$ .	Dichlormethane, or methylene dichloride.
$\text{CHCl}_3$ .	Trichlormethane, or chloroform.
$\text{CCl}_4$ .	Tetrachlormethane, or carbon tetrachloride.

Bromine acts similarly to chlorine but less vigorously. As stated in the previous chapter, this substitution of hydrogen by chlorine is always accompanied by a liberation of hydrochloric acid. It was, in fact, the hydrochloric acid evolved during the burning of paraffin candles that had been bleached by chlorine that led Dumas in 1834 to his "*substitution theory*," the keystone to the present views on the mutual replacement of atoms or their equivalent. The formation of methyl chloride from methane is represented by the equation:—



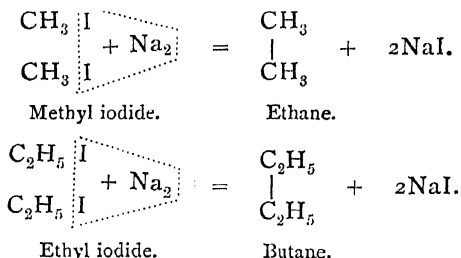
The chlorine, according to Dumas, takes the place of or *substitutes* the hydrogen. Berzelius, who based all his views regarding chemical change on the electro-chemical character of the reacting substances, strenuously opposed this theory; the idea of electro-negative chlorine replacing electro-positive hydrogen appeared to him as impossible and absurd. The conditions of substitution and the chemical and physical relations of the resulting products to the original compound have, however, amply confirmed Dumas' views. These substitution products serve as the starting-point for the preparation of many derivatives of the hydrocarbons; their relation to the latter is shown in the *inverse substitution* of the chlorine by hydrogen. Nascent hydrogen, generated from zinc and acid, can effect this change:—



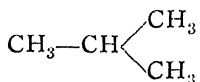
The reaction is easily carried out and is a useful method for the preparation of pure hydrocarbons.

In speaking of the nature of the double linking in ethylene, it was stated that when such univalent radicals as methyl or ethyl are liberated from compounds they never separate in the free state, but combine with a second similar radical. This is the rationale of another method for preparing paraffin hydrocarbons. Methyl and

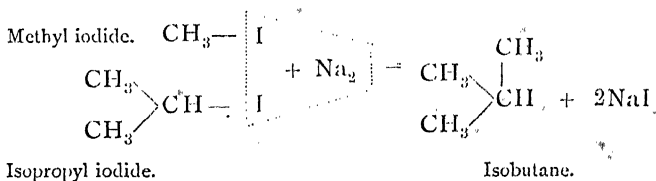
ethyl iodide are the analogues of methyl and ethyl chloride, substitution products of their respective hydrocarbons, having the formulæ  $\text{CH}_3\text{I}$  and  $\text{C}_2\text{H}_5\text{I}$ . Metallic sodium, has a great affinity for iodine, forming sodium iodide,  $\text{NaI}$ ; when brought in contact with methyl or ethyl iodide under suitable conditions, the sodium combines with their contained iodine, liberating the radicals  $\text{CH}_3$  and  $\text{C}_2\text{H}_5$  respectively. By mutual saturation ethane,  $\text{C}_2\text{H}_6$ , and butane,  $\text{C}_4\text{H}_{10}$ , result as the products of the reactions:—



Such a method of synthesis affords the means of proving the structure of hydrocarbons, as, for instance, in the case of the isomer of butane,  $\text{C}_4\text{H}_{10}$ , to which, from the law of the linking of atoms, the structural formula:—



is assigned.<sup>1</sup> Since the above reaction can be equally well applied to a mixture of iodides, a compound of this formula should result by allowing sodium to act upon a mixture of methyl iodide and isopropyl iodide, thus:—



<sup>1</sup> Cf. chap. ii. p. 30.



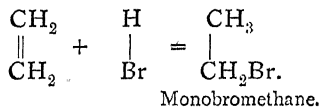
The product formed is identical with the isomer of normal butane in all its properties. This synthesis is a satisfactory proof of the correctness of the above formula. The only criticism which could be made in opposition to this conclusion would be that some change might have occurred in the arrangement of the atoms during the reaction. Such changes, generally called molecular rearrangements, do occur at times, and on more than one occasion have led to erroneous deductions, but still they are to be regarded as the exceptions, not the rule. They arise usually during violent or high temperature reactions, and are recognised by the discordant results of what should otherwise be analogous changes. As a matter of fact, the isopropyl group does often change into the normal propyl group and vice versa, but were such a molecular rearrangement to occur in the above reaction, normal butane, the structure of which has been satisfactorily proved, would result. This is not the product of the reaction, and hence the formula indicated by the law of the linking of atoms is supported by this synthesis.

Gradations in physical properties are characteristic of the paraffins as of all homologous series. The first four members from methane  $\text{CH}_4$  to butane  $\text{C}_4\text{H}_{10}$ , are gases at the ordinary temperature; normal butane boils at  $+1^\circ$ .<sup>1</sup> From normal pentane  $\text{C}_5\text{H}_{12}$ , which boils at  $37^\circ$ , to pentadecane  $\text{C}_{15}\text{H}_{32}$ , which boils at  $270^\circ$ , and melts at  $10^\circ$ , they are liquids, the boiling points of which increase in a regular gradation throughout the series; the higher homologues, the constituents of vaseline and paraffin wax are solids. The specific gravity increases gradually with the molecular weight up to the solid hydrocarbons and then remains approximately constant, when determined at the melting point. Such generalities are of value as an aid in indicating the position of a hydrocarbon in a series, since the differences in the percentage composition of the higher members is very small—in fact, less than the average error of analysis. For example,  $\text{C}_{15}\text{H}_{32}$  contains 84.80 per cent. of carbon and 15.20 per cent. of hydrogen, whilst the next higher homologue,  $\text{C}_{16}\text{H}_{34}$ , contains 84.86 per cent. of carbon and 15.14 per cent. of hydrogen.

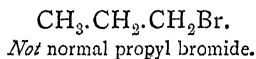
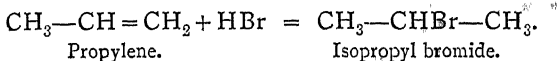
<sup>1</sup> All temperatures are given in Centigrade degrees.

## THE ALIPHATIC HYDROCARBONS.

*The Ethylene Series of Hydrocarbons.*—Ethylene and its homologues show similar gradations to the paraffin series in their physical properties. Their chemical character is entirely different; they are very reactive substances, especially in their capability of combining directly with two atoms of hydrogen, bromine, or chlorine to form saturated compounds. In these combinations the double link between the two unsaturated carbon atoms is attacked and the two atoms are added symmetrically as already stated. Halogen acids, especially hydriodic and hydrobromic acid, also combine directly, forming the mono-substitution products of the paraffins; with ethylene and hydrobromic acid, for instance, monobromethane results:—

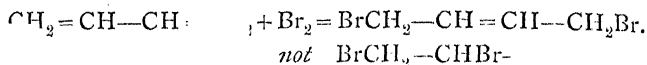


Since ethylene is a symmetrical molecule, it is immaterial with which of the two carbon atoms the bromine of the hydrobromic acid combines; in either case the same product must be formed. But with the unsymmetrical homologues of ethylene this is not the case. Propylene  $\text{C}_3\text{H}_6$ , for instance, forms isopropyl bromide, thus:—



The halogen atom attaches itself to that carbon atom which is combined with the least hydrogen. This course of the reaction is general for the series, and has been of value in elucidating the structure of some of the higher members. With the more complex unsaturated compounds, typically those containing two adjoining pairs of double bonds, or, as they are often called, "ethylene linkings," the course followed in the formation of addition products is less simple. The product of the action of bromine on compounds of the type  $\text{CH}_2=\text{CH—CH=CH}_2$  is a compound in which one atom of halogen is attached to each of the end carbon atoms, not to adjacent carbon atoms, as is the case with compounds containing only

one ethylene bond, with the result that a new double bond is formed in the molecule, thus:—



From this it is evident that the two double bonds exercise some mutual influence. It may be that the addition primarily follows the normal course, and that the final product is formed by a secondary change. Another view is that the two intermediate carbon atoms are inactive in respect to the formation of addition products because their unsaturated valencies mutually saturate each other, so that the unsaturation of the molecule is only manifested at the ends of the chain much on the same lines as the origin of the two poles of a magnet. After the addition of the molecule of bromine a readjustment of the linkings is necessary, and a new double bond must result. This latter interpretation, together with some suggestive ideas on the nature of the unsaturated valencies of elements, has been put forward by Thiele;<sup>1</sup> it has certainly brought a number of apparently divergent reactions into line, and as a theoretical speculation has thus served a useful purpose.

Whilst recognising the importance of such intramolecular transformations, it is to be borne in mind that they are the exception and not the rule. Unless there is any reason to the contrary, it may generally be assumed that the structure of the molecule remains intact.

*The Acetylene Series of Hydrocarbons.*—Acetylene itself,  $\text{C}_2\text{H}_2$ , is the type of all compounds which contain two or more carbon atoms united by a triple bond. As stated above, this condition of combination is most satisfactorily represented by the following formula for acetylene:—



This hydrocarbon is of special interest, since it can be directly formed from its elements. Recent researches show that the formation of acetylene is just perceptible at  $1,700^\circ$ , and increases progressively up to about  $2,500^\circ$ ;<sup>2</sup>

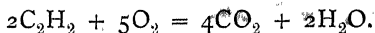
<sup>1</sup> *Annalen*, 1899, cccvi. 87. Cf. also Knoevenagel, *Berichte*, 1903, xxxvi. 2803.

<sup>2</sup> Pring and Hutton, *J. Chem. Soc.*, 1906, lxxxix. 1591.

small quantities of methane are formed at the same time. The synthesis of acetylene is best carried out at the higher temperature of the electric arc by passing hydrogen through a globe in which the arc is completed between two carbon poles, when the issuing gas contains a considerable proportion of acetylene. The presence of an excess of hydrogen is an important condition in the formation of acetylene. Since acetylene can be readily converted into ethylene and ethane, and these by successive stages into a large number of organic compounds such as alcohol, acetic acid, tartaric acid, etc., the syntheses of these compounds, starting from the elements carbon and hydrogen, are possible. Such complete syntheses were first carried out by Berthelot.<sup>1</sup>

Although acetylene results directly from its elements at the temperature of the electric arc, it is much less stable at lower temperatures. When passed through a tube heated to bright redness it is almost completely decomposed into its elements, and at lower temperatures it is converted into more stable hydrocarbons, such as benzene. The stability of acetylene at very high temperatures is probably conditioned by a decrease in the valency of the carbon atom when strongly heated. Many of the elements exert a lower valency at high temperatures,<sup>2</sup> as is shown by the dissociation of their compounds.

Acetylene, like ethane and ethylene, is a gas. It is condensed to a liquid by a pressure of 83 atmospheres at a temperature of 18°; in the liquefied state it is very unstable and liable to sudden decomposition with explosive violence. This is due to the strained condition of the carbon linkings, and confirms the instability of such unsaturated compounds as compared with compounds such as methane. It burns with an intensely luminous flame, forming carbon dioxide and water according to the following equation:-



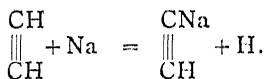
When mixed with oxygen or air, in the proportion indicated by this equation, and fired, either by a naked light or

<sup>1</sup> *Chimie organique fondée sur la Synthèse*, 1860, and *Les Carbures Hydrogène*, 1851-190

<sup>2</sup> Cf. "Die Valenzlehre," Hinrichsen, *Sammlung chem. und technische Vorträge*, 1902, p. 34, published by Enke, Stuttgart.

by an electric spark, it explodes with terrific violence, and a very large excess of oxygen or air is necessary to overcome the explosive character of its combustion. A mixture of acetylene with only one-fourth of its own volume of oxygen explodes with great violence when fired by the electric spark.

Acetylene and all trebly-linked carbon compounds behave as doubly unsaturated substances, as previously indicated; the addition of the added elements or groups follows fairly definite lines, as in the case of the ethylene series of hydrocarbons. The most marked characteristic of these compounds is their power of forming metallic compounds. When metallic sodium is heated in a confined volume of acetylene, the latter disappears, a brown crust is formed over the sodium, and about half the original volume of gas is left. This residual gas is hydrogen, and the brown crust on the surface of the sodium is the metallic derivative of acetylene, which under special conditions can be obtained as a white powder; it is formed according to the equation:—

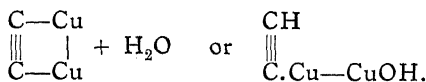


Mono-sodium acetylide.

At a higher temperature the second atom of hydrogen can be replaced, and di-sodium acetylide,  $\text{C}_2\text{Na}_2$ , is formed as a white amorphous mass. Potassium acts similarly, but it is more remarkable still that heavy metals, especially copper and silver, which are in general much less reactive than sodium or potassium, form analogous compounds. The copper compound is readily obtained as a characteristic brown precipitate by passing acetylene through an ammoniacal solution of a cuprous salt; the reaction is so delicate that 0.01 per cent. of acetylene can be detected by its means in a gaseous mixture. The silver compound, which is yellowish white in colour, is similarly formed. Both regenerate acetylene when treated with dilute acids, and explode upon heating or percussion, the silver salt being by far the more explosive of the two. All hydrocarbons containing trebly-linked carbon atoms, and no others, form these explosive metallic derivatives. Their

## THE ALIPHATIC

constitution is still the subject of discussion, as several grades of these substances appear to exist. The simple acetylene compounds have the formulæ  $C_2H_2.Cu_2O$  and  $C_2H_2.Ag_2O$ , and the generally accepted structure for the former is one or other of the following:—

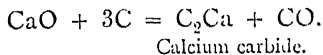


The number of these metallic compounds has been largely increased during the last few years by employing the electric furnace in their preparation, and since by this means their production is possible on a manufacturing scale, considerable practical interest has been added to their theoretical importance. Foremost amongst these newer derivatives of acetylene stands calcium carbide, essentially on account of its serving as the starting-point for the technical preparation of acetylene for illuminating purposes. They are usually classed together as the metallic carbides, being compounds of a metal and carbon like sodium acetylides.

*The Metallic Carbides and their preparation in the Electric Furnace.*—The application of the electric furnace to the preparation of acetylene derivatives is an important extension of the methods for the preparation of the simpler organic compounds. The carbides may be justifiably included in either the organic or inorganic branch of chemistry, and they offer interesting points of study to both divisions. They appeal to the organic chemist as the products of the direct combination of carbon with other elements, which by their decomposition give rise to hydrocarbons. They vary greatly in their stability, some being readily and completely decomposed by water, whilst others are amongst the most stable compounds known; this difference is dependent on the chemical character of the elements with which the carbon is combined.

*Calcium carbide* is prepared by passing a powerful electric current through a mixture of coke and lime. The current serves only as a source of heat, and has no electrolytic action upon the substances concerned; the high temperature thus generated, which is practically that

of the electric arc ( $3700^{\circ}$ ), effects the combination. This takes place with the evolution of carbon monoxide according to the equation:—



A great variety of furnaces have been designed for electro-thermic processes of this kind. The form shown in Fig. 1

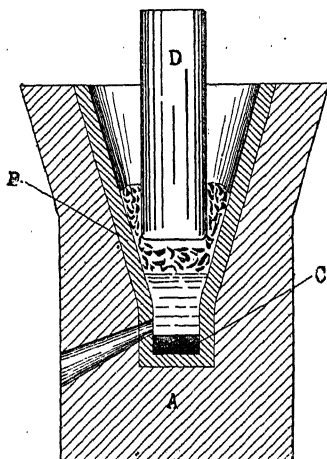


FIG. 1.

illustrates the method of working adopted in the manufacture of calcium carbide. The material of the furnace consists of a fire-brick casing (A), with a lining of magnesia (B), shaped so as to provide a conical vessel for the reception of the mixture to be treated; a tapping hole is provided at the bottom of the furnace. The electrodes for conveying the current consist of a carbon plate (C) placed on the bed of the furnace and an adjustable carbon (D). The mixture of coke and lime is fed in from the top of the

furnace. The temperature generated on the completion of the electrical circuit between the electrodes is sufficiently high to fuse the carbide as it is formed, so that it can be run off through the tapping hole whilst still in a molten state; this allows the process to be worked continuously. The carbon monoxide liberated in the decomposition is drawn off through a side flue by means of a fan. A current of some 2000 ampères and 70 to 100 volts is employed, about 6000 to 8000 horse-power hours being required for the preparation of a ton of carbide.<sup>1</sup>

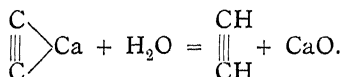
<sup>1</sup> The manufacture of Calcium carbide is described in:—

*Acetylene*. Vivian B. Lewis. 1900.

*Electric Furnaces and their Industrial Applications*. J. Wright. 1904.

Electric furnaces for experimental purposes are similarly arranged. In some of these blocks of lime are used in preference to fire-brick for the material of the furnace, whilst in others the substances to be heated are placed in crucibles or in tubes of carbon, thus avoiding the direct action of the carbon of the electrodes on the materials to be heated. Also, the position of the electrodes is varied according to circumstances, as it is preferable in some cases to have them horizontal or at an angle, instead of vertical.<sup>1</sup>

Calcium carbide is quite white when pure, but as ordinarily prepared it is a grey, friable solid, very readily decomposed by water with the evolution of acetylene according to the equation :—



By suitable mechanical contrivances this decomposition can be regulated, according to the rate of consumption of the liberated gas, as required for illuminating purposes. When burned in specially constructed burners so as to effect complete combustion, acetylene gives a brilliant light, equivalent to 240 standard candles when burned at the rate of five cubic feet per hour. This is about twelve times the illuminating power of good coal gas. There are, however, many difficulties in the supply of the gas on a large scale, apart from that of cost, but for isolated districts where no supply of an illuminant is at hand, and also for portable lamps, it undoubtedly possesses advantages on account of the readiness with which it can be prepared *in situ*.

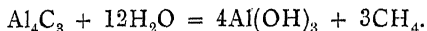
Moissan has shown that a number of other carbides can be similarly prepared.<sup>2</sup> The alkalis and alkaline earths all yield carbides which are readily decomposed by water with the evolution of acetylene, like carbide of calcium. The carbides of aluminium and beryllium,  $\text{Al}_4\text{C}_3$  and  $\text{Be}_2\text{C}$ , are equally readily decomposed, but the resulting hydrocarbon is methane in place of acetylene.

<sup>1</sup> Cf. *The Electric Furnace*. H. Moissan; trans. by A. T. de Moulpiéd, 1904.

<sup>2</sup> *Loc. cit.*



Were there any technical application for methane, aluminium carbide would form an accessible material for its preparation; the decomposition takes place according to the equation:—



The carbides of manganese, uranium, and of certain rare metals have also been obtained; these undergo a more complex decomposition when treated with water, yielding varying proportions of methane, acetylene, ethylene and hydrogen. Uranium carbide forms, in addition, a small quantity of liquid and solid hydrocarbons the nature of which has not yet been ascertained.

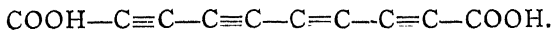
Certain non-metals also give rise to carbides, which differ from the above in being exceptionally stable compounds, unaffected by water or by strong acids, and undergoing decomposition only when heated with powerful oxidising agents at a high temperature. Silicon carbide,  $\text{SiC}$ , is the most important of these; it is prepared in the electric furnace from a mixture of coke and sand, and forms magnificent lustrous crystals which approach the diamond in hardness. Under the name of *carborundum* it has been successfully introduced as an abrasive.<sup>1</sup>

*Further Considerations regarding the Structure of Unsaturated Compounds.*—The structure of the saturated compounds of the aliphatic group, based on the law of the linking of atoms, is clear and complete; no further hypotheses are involved, and any speculations regarding the methods of linking between their carbon atoms can be readily put to the test of direct experiment.

The constitutional differences between unsaturated and saturated compounds are fairly satisfactorily represented by means of double or triple bonds; this is a ready expression of their relative chemical character. The real conditions of combination which such multiple linkings represent is, however, far more difficult to ascertain. From the formulæ for ethylene and acetylene, as compared with that of ethane, the conclusion might be drawn that the carbon atoms in the former are united to each other by

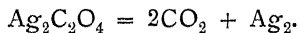
<sup>1</sup> Cf. "The Carborundum Furnace," F. A. J. Fitzgerald: *Electrochemical Industry*, 1906, iv. 53; and "The Manufacture and Uses of Carborundum," *J. Soc. Chem. Ind.*, 1897, xvi. 863.

a stronger force than in the saturated molecule ethane; that two singly-linked carbon atoms represent a less stable condition than when they are doubly-linked as in ethylene, and that the two trebly-linked atoms in acetylene point to it as the most stable of the three compounds. But this is not in accord with the chemical character of the unsaturated hydrocarbons. Unsaturated compounds are typically less stable than saturated, and are especially liable to change at that part of their molecule where there is a double or triple link between the carbon atoms. Compounds containing trebly-linked carbon atoms are also characterised by their explosive nature. Silver and copper acetylide explode readily when heated, and when the number of trebly-linked carbon atoms in a molecule is increased the instability becomes markedly more pronounced. An acid, for instance, is known containing four pairs of trebly-linked carbon atoms:—



Tetra-acetylene dicarboxylic acid.

This substance is highly explosive, and is decomposed in a few minutes on exposure to light. Another factor may, however, influence the instability of such compounds—namely, the ease with which they can break up into simple, stable molecules. For instance, under certain conditions silver oxalate, which contains two singly-linked atoms of carbon, is violently explosive; but it can break up completely into the simple molecules of silver and carbon dioxide as represented by the equation:—



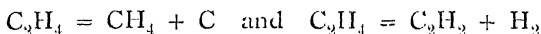
and this is probably the reason for its explosive character. Similarly, the above acid can break up almost completely into carbon and carbon dioxide.

The formation of acetylene at the temperature of the electric arc appears to stand in direct opposition to the relative instability of unsaturated compounds. Its stability at high temperatures is shown not only by its direct formation from carbon and hydrogen, but also by the fact that it is produced by the incomplete combustion of other hydrocarbons, and by subjecting many organic compounds,

such as ethyl alcohol, and ether, to prolonged heating at  $1000^{\circ}$ . As already stated, the presence of a large excess of hydrogen is essential for the formation of acetylene in the electric arc, and it was until recently regarded as the only hydrocarbon that could be thus obtained directly from the elements. Accurate experiments by Bone and Jordan<sup>1</sup> have, however, proved that methane and ethane, as well as acetylene, are formed by the direct union of carbon and hydrogen in the electric arc, and that by continuing the passage of the arc a state of equilibrium between the hydrogen, methane, ethane, and acetylene is finally established. This same equilibrium between the four gases is reached when the electric arc is similarly produced in an atmosphere of either methane or of acetylene, and corresponds to a mixture containing from 7 to 8 per cent. of acetylene, 1.25 per cent. of methane, 0.75 per cent. of ethane, and 90 to 91 per cent. of hydrogen. At a lower temperature,  $1200^{\circ}$ , methane alone results by the direct combination of carbon and hydrogen, and this to the extent of about one per cent. of the hydrogen present; no acetylene or other unsaturated hydrocarbon is formed at this temperature. The explanation of the formation of acetylene at the temperature of the electric arc is to be sought in the influence of heat on the decomposition of hydrocarbons. The tendency of increasing temperature is towards their complete decomposition into carbon and hydrogen, probably, as already stated, owing to a decrease in the valency of carbon; this involves a gradual loss of hydrogen, and therefore hydrocarbons, rich in carbon and poor in hydrogen, such as acetylene, are to be expected at high temperatures as intermediate products. The complete decomposition is prevented by the presence of an excess of hydrogen, just as the presence of chlorine stays the dissociation of phosphorus pentachloride into the trichloride and free chlorine. This view is indicated by the equilibrium established when either methane or acetylene is heated in the electric arc; in both cases carbon and hydrogen are separated, but acetylene, methane, and ethane are formed respectively at the same time. The absence of ethylene under these conditions

<sup>1</sup> *J. Chem. Soc.*, 1897, lxxi. 26; and 1901, lxxix. 1042. Cf. also Pring and Hutton, *J. Chem. Soc.*, 1906, lxxxix. 1591.

is most probably accounted for by the fact that its composition allows of the ready formation of methane and free carbon, or of acetylene and hydrogen, according to the equations:—



The occurrence of such decompositions is supported by the observation that both methane and acetylene are formed when ethylene is exploded with an insufficiency of oxygen.<sup>1</sup> Also, recent experiments by Bone and Coward<sup>2</sup> have proved that methane is formed by the thermal decomposition of ethane, ethylene, and acetylene in an atmosphere of hydrogen at temperatures between 800° and 1200°, and that it is by far the most stable of these four hydrocarbons between these temperatures.

The evidence as to the condition of combination represented by a double or treble bond points to a less stable molecular condition than exists with singly-linked carbon atoms, and to the presence of some residual combining-power or "residual affinity" in molecules containing such multiple linkings. Were the real nature of the force known which holds the elements of a molecule together, the force of *chemical affinity*, a more complete and quantitative relationship of these different methods of linking would be possible. The knowledge regarding the nature of chemical affinity is, however, as yet, too purely speculative to be of value in elucidating these relations; nor are there any means by which, despite this ignorance of its nature, it can be measured directly. By indirect means, however, it is possible to measure the energy manifested in the formation and decomposition of molecules—chemical energy or chemical affinity. Like all other forms of energy, it plays its part in the great principle of the conservation of energy; it can be transformed into heat, kinetic energy, or electrical energy, or can result from any of these, and in all these changes there is a definite quantitative relationship. In order to measure chemical energy indirectly, the only available method, it must be transformed into some other kind of energy, and as it passes most easily and completely into heat, its measure-

<sup>1</sup> Lean and Bone, *J. Chem. Soc.*, 1892, li. 873.

<sup>2</sup> *J. Chem. Soc.*, 1908, xciii. 1197

ment is effected in terms of the heat changes that accompany chemical processes.

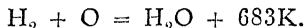
*Thermochemistry*<sup>1</sup> is the branch of the science that deals with such measurements; it gives a means of approaching a relative estimate of the forces concerned in the formation of saturated and unsaturated compounds.

*The Thermochemical Relations of Saturated and Unsaturated Hydrocarbons.*—The quantities of heat evolved or absorbed in chemical changes can be measured either directly or indirectly. In the formation of inorganic compounds the changes involved are, as a rule, complete and rapid; in such cases a direct measurement of the accompanying heat changes can be made. The reactions concerned in the formation of organic compounds, on the other hand, proceed gradually, generally at a high temperature, and are usually incomplete owing to the occurrence of secondary reactions, which lead to the formation of by-products; hence indirect thermochemical methods must be employed. Of these the only one used in practice is that of complete combustion. This rests upon a fundamental principle of all thermochemical processes, the law of "constant heat summation" (Hess, 1840), according to which the development of heat in chemical reactions is alone dependent upon the initial and final stages; it does not matter in however many stages this heat may be communicated, the final result is the same. It is thus possible to arrive at the *heat of formation* of organic compounds by determining the heat evolved in their combustion. Heat quantities are measured in terms of the *calorie*; one calorie is the quantity of heat required to raise the temperature of one gram of water from 0° to 100° Centigrade, and it is represented in thermochemical equations by the letter K.

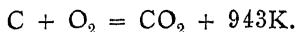
The products of complete combustion of hydrocarbons are carbon dioxide and water; from the above it is necessary to know the heat of formation of the latter compounds, in order to arrive at that of the former.

<sup>1</sup> An account of Thermochemistry will be found in the following works:—*The Elements of Thermal Chemistry*, Muir and Wilson, 1885; *Outlines of General Chemistry*, Ostwald, translated by Walker, 1890; *Thermochemistry*, J. Thomsen, translated by K. A. Burke, 1907; *Introduction to Physical Chemistry*, Walker, fourth edition 1907.

When hydrogen and oxygen combine to form water, 683 calories of heat are evolved for every 2 grams of hydrogen burned. This is expressed by the thermochemical equation:—

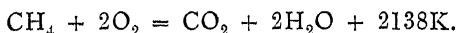


The water formed is retained in the liquid state at a mean laboratory temperature of 18°; in all thermochemical changes it is necessary thus to state the exact conditions under which the measurements are made. The formation of carbon dioxide from the purest form of carbon, the diamond, is accompanied by an evolution of 943 calories for every 12 grams of carbon burned (*i.e.*, one gram equivalent):—

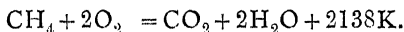
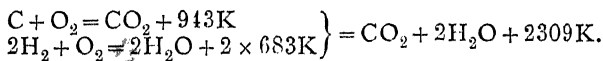


The intrinsic molecular energy of the elements carbon, hydrogen, and oxygen is regarded as zero in these equations; there is no means of determining it. The values given above for the heat of formation of carbon dioxide and water represent only the difference between the intrinsic energies of the compounds and that of the component elements.

In the combustion of methane 2,138 calories are evolved for every gram-molecule equivalent (16 grams) burned; the complete energy equation for the change is therefore:—

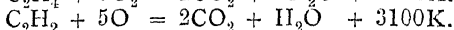
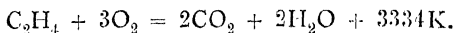


Since, according to the law of constant heat summation, it is immaterial for the total thermic value of the change whether these products are formed directly from the elements or indirectly through hydrocarbons, the difference between the heat of combustion of methane and that of its elements must be equal to the heat of formation of a gram-molecule of the former from solid carbon and hydrogen gas. This is calculated as follows:—

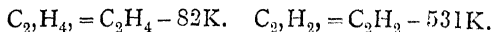


*Heat of formation of methane  
from the elements*  $\text{C}, 2\text{H}_2 = \text{CH}_4 + 171\text{K},$

Many unsaturated hydrocarbons have a greater heat of combustion than the carbon and hydrogen contained in them. The thermochemical equations for the combustion of ethylene and acetylene are:—

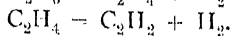
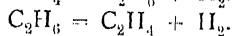
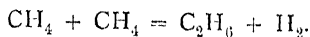


Subtracting the calories or heat evolved in the formation of the number of molecules of carbon dioxide and water that result in each case, the following negative values are left as representing the heats of formation of these hydrocarbons:—



These quantities of heat are therefore absorbed in the formation of ethylene and acetylene from their elements. Compounds which thus require heat for their formation are called *endothermic*; they are always comparatively unstable, decompose with the evolution of heat, and can only be prepared directly from their elements at a high temperature. *Exothermic* compounds, on the other hand, the formation of which is accompanied by an evolution of heat, such as methane and by far the largest proportion of all chemical compounds, are stable at ordinary temperatures, but are often decomposed on heating.

These preliminary considerations will suffice to indicate the method by means of which the chemical energy of organic compounds is measured. In order to arrive at a comparison of the energies with which singly, doubly, and trebly linked carbon atoms are held together, it is necessary to study the thermic changes that occur in the passage from one to the other of such conditions of combination amongst a suitably selected series of compounds. The most complete comparison is given by calculating such heat changes as accompany the loss of two hydrogen atoms in the formation of, say, ethane from two molecules of methane, ethylene from ethane, and acetylene from ethylene respectively, as represented by the equations:—



These reactions are not feasible in practice, but it is nevertheless possible to ascertain the changes of energy by which they would be accompanied.

In the first reaction, two carbon atoms not previously united become linked by a single bond, in the second singly-linked carbon atoms become linked by a double bond, and in the third the double bond passes into a triple bond. In accepting such changes as a basis for the comparison, it is assumed that the force with which an atom of hydrogen is united to one of carbon is actually the same whatever the conditions of combination of the remaining carbon or other atoms of the molecule. Several methods have been adopted for the calculation of the heat changes involved in such reactions,<sup>1</sup> and although the resulting figures for the relative intrinsic energy of singly, doubly, and trebly-linked carbon atoms are not free from criticism, they may be accepted as proving beyond a doubt that the force with which doubly or trebly-linked carbon atoms are held together is not two or three times as great respectively as that acting between two singly-linked carbon atoms. As a matter of fact, it is considerably less, and, further, the difference between the force uniting singly and doubly-linked carbon atoms is not the same as that between doubly and trebly-linked atoms. This relative estimate allows of the definite conclusion that there is a constitutional difference between single and multiple linking, which is not apparent from purely chemical considerations, and that the successive formation of single, double, and triple bonds is not a repetition of one and the same process. It goes but a short way, however, towards the full solution of the problem; this must await a more thorough knowledge of the nature of chemical affinity. It will be shown in Chapter XII. that considerable light is thrown on the instability of the unsaturated compounds by a study of the tension which occurs in the carbon molecule when the direction of the affinities deviates from the normal, as based on the stereochemical relations of organic compounds.

<sup>1</sup> Cf. Dieffenbach, *Z. physik. Chem.*, 1890, v. 569; Horstmann, *Berichte*, 1888, xxi. 2,211; Thomsen, *Z. physik. Chem.*, 1887, i. 369, and 1891, vii. 55; Van't Hoff, *Lectures on Theoretical and Physical Chemistry*, 1899, part iii. p. 100.



## CHAPTER V.

### THE CYCLIC HYDROCARBONS.

*Saturated Cyclic Hydrocarbons:*—Trimethylene, its structure and relation to aliphatic hydrocarbons.

*The Aromatic Compounds:*—Benzene.—The substitution products of benzene: isomerism amongst aromatic compounds.—The structure of benzene.—The bearing of the physical properties of benzene and of its derivatives on the structure of the benzene ring.—The orientation of aromatic compounds.

CYCLIC compounds comprise the substances the molecules of which contain a closed chain or ring of carbon atoms. As already stated, they may be conveniently grouped in two divisions: the *Isocyclic compounds*, in which the ring consists of like atoms only, and the *Heterocyclic compounds*, in which, together with carbon, other atoms, such as nitrogen, sulphur, or oxygen, are present.

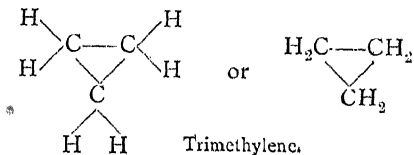
The structure of the latter is essentially based upon that of the isocyclic compounds, and apart from intrinsic differences that naturally arise from the substitution of the carbon atoms by other elements, the study of the most important heterocyclic substances has in many respects consisted in an application of the knowledge derived from the investigation of isocyclic compounds. For this reason, as also on account of the more simple structure of isocyclic compounds, this chapter will be restricted to their consideration.

In aliphatic compounds there is no limit to the number of carbon atoms that are capable of uniting to form a continuous chain; saturated hydrocarbons up to  $C_{60}H_{132}$  are known. Cyclic compounds offer a marked contrast in this respect. Compounds are known containing rings of 3, 4, 5, 6, 7, and 8 carbon atoms, but it is unlikely, as the result of experiment as well as of theoretical deductions, that closed-chain compounds with more than eight carbon

atoms in one ring can exist, although much larger heterocyclic rings are known.<sup>1</sup> Each of these closed chains of carbon atoms, combined with hydrogen as hydrocarbons, is the starting-point for an homologous series, and therefore the range and number of the isocyclic substances is in no way inferior to that of the aliphatic compounds.

By far the best known and most thoroughly studied of these cyclic compounds are those containing a ring of six carbon atoms, benzene and its derivatives. These constitute the well-characterised group of *aromatic or benzenoid compounds*, and until about thirty years ago very few other cyclic compounds were known. More recent investigations have, however, introduced many methods for preparing other closed-chain compounds of great variety and complexity. These methods have led to the synthesis of substances of technical value, and in addition have had an important bearing on many points of theoretical interest, such as the stereochemistry and other isomeric relations of cyclic compounds.

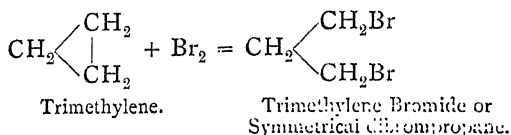
*Saturated Cyclic Hydrocarbons.*—Trimethylene is the simplest cyclic hydrocarbon. It has the formula  $C_3H_6$ , and is therefore an isomer of propylene, the homologue of ethylene; like propylene, it is a gas which burns with a brightly luminous flame. Although it has the empirical formula of an unsaturated compound, its chemical behaviour is far more akin to that of a saturated aliphatic substance. It is considerably more stable in every respect than ethylene; chlorine forms a substitution, not an addition product, and it is more stable towards oxidising agents than unsaturated aliphatic compounds. As a closed-chain compound, there is only one possible formula for trimethylene:—



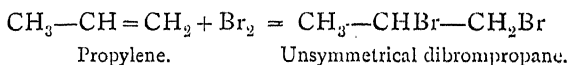
<sup>1</sup> Cf. R. Meyer, *Annalen*, 1906, cccxlvii. 17.

The divalent group  $\text{CH}_2$  is called *methylene*, hence the above nomenclature.

Although trimethylene forms a substitution product with chlorine, it can, under favourable conditions, be converted into saturated open-chain compounds by addition, as is the case with ethylene and its homologues; but the structure of the resulting products is the most satisfactory proof that the carbon atoms in the trimethylene molecule are linked together in a closed chain by single bonds. It is, for instance, far more stable towards bromine than its isomer propylene, but in presence of sunlight combination occurs and trimethylene bromide results, a compound having the added bromine atoms attached one to each of the end carbon atoms of the propane chain, and which can be reconverted into trimethylene by the action of sodium:—



Propylene, on the other hand, combines most readily with bromine, like all unsaturated compounds, but the added bromine atoms are attached to adjacent carbon atoms:—

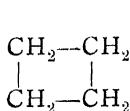


This reaction at once points out the difference in structure between the two hydrocarbons.

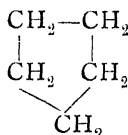
Another reaction characteristic of the unsaturated hydrocarbons is that of potassium permanganate in alkaline solution, which oxidises the hydrocarbon, attacking the ethylene linking. When this reaction is applied to trimethylene, the oxidation only takes place slowly, indicating a greater stability than is found in the unsaturated compounds. The fact that oxidation does occur shows, however, that trimethylene does not possess quite the same degree of stability as the saturated aliphatic hydrocarbons.

The simplest cyclic compounds containing four and five

carbon atoms are the hydrocarbons *tetramethylene*,  $C_4H_8$ , and *pentamethylene*,  $C_5H_{10}$ :—

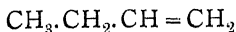


Tetramethylene.

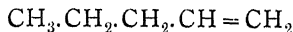


Pentamethylene.

Like trimethylene compounds, these do not possess the characteristics of unsaturated molecules, although they are isomeric with butylene and pentylene respectively:—



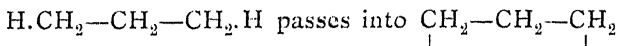
Butylene.



Pentylene.

They are, in point of fact, considerably more stable than the trimethylene group, but, like the latter, present many analogies in their chemical behaviour to saturated aliphatic compounds.

These three hydrocarbons contain two hydrogen atoms less than the corresponding compounds of the paraffin series, but they are saturated compounds, since the carbon valencies that would otherwise be free serve to unite the three, four, or five carbon atoms in the form of a closed chain. The formation of such closed chains, which involves a loss of two atoms of hydrogen, is not accompanied by any marked change in the chemical character either of the hydrocarbons or of their derivatives, and hence the name of *Alicyclic compounds* has been given to them. When, therefore, the group:—

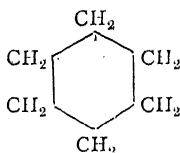


Propane,

Trimethylene,  $C_3H_6$ ,  
or Cyclo-propane.

the typical properties of an aliphatic compound, its "aliphatic character" is preserved. The name *Cyclo-propane* expresses this relation.

The six carbon atom analogue of these alicyclic compounds is hexamethylene,  $C_6H_{12}$ :—



Hexamethylene.

This compound is of special interest as the reduction product of benzene,  $C_6H_6$ , which latter appears at once, from the above considerations, as an unsaturated cyclic compound.

✓ *The Aromatic Compounds: Benzene.*—From the time of Liebig and Wöhler's investigations on the "Radical of Benzoic Acid" onwards, numerous experimental inquiries were carried out amongst aromatic compounds, but no attempt was made to deduce their constitution until the publication of Kekulé's benzene theory in 1865. This theory was the crowning achievement of the new chemistry initiated by Kekulé, the chemistry of the structure of compounds based on the doctrine of the linking of atoms. Kekulé's conception of benzene as a closed chain of six carbon atoms threw a flood of light on the whole group of aromatic compounds. The special characteristics of benzene and its homologues, the isomeric relations of their derivatives and the fundamental differences between aromatic and aliphatic compounds were explained and correlated by the new hypothesis. Under its influence the chemistry of the aromatic compounds has developed to one of the most accurately investigated and fruitful branches of the whole of chemistry.

Benzene was discovered by Faraday in 1825,<sup>1</sup> amongst the products of distillation of oils and fats, prepared by the "Portable Gas Company." This company distributed compressed oil-gas for illuminating purposes in iron cylinders, which were placed in the cellars of the houses and there attached to the pipes for use. In order to fill the cylinders the gas was passed from the gas-holders under a

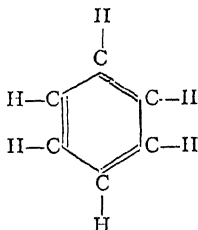
<sup>1</sup> *Phil. Trans.*,

pressure of about thirty atmospheres into a large, strong receiver and thence by pipes into the portable vessels. A considerable quantity of liquid products was found to accumulate in the receiver. These were examined by Faraday, who succeeded in isolating benzene from the mixture and in determining its composition and physical properties.

To-day, coal tar is the chief source of benzene and its homologues.<sup>1</sup> Benzene is a colourless, highly refractive liquid, lighter than water, and boiling at  $80^{\circ}.2$ . When cooled in a freezing mixture it solidifies to a crystalline mass which melts at  $5^{\circ}.4$ . The most marked chemical characteristic of benzene is its stability. It is only with the very greatest difficulty that it can be resolved into simpler substances, whilst it remains as the final decomposition product of its numerous homologues and derivatives. Moreover, as compared with the saturated aliphatic hydrocarbons, it is a very reactive substance. Nitric acid and sulphuric acid readily form substitution products, and both chlorine and bromine act upon it more easily than they do upon the paraffins, to produce halogen substitution compounds. On the other hand, benzene behaves similarly to an unsaturated, open-chain hydrocarbon under certain conditions. For instance, when chlorine is passed into benzene at a moderately high temperature, or in presence of direct sunlight, an addition product of the formula  $C_6H_6Cl_6$  results—*benzene hexachloride*—though the addition takes place very much less readily than in the case of the unsaturated aliphatic compounds. Many similar addition compounds of benzene and its homologues are known and, as in the case of unsaturated aliphatic compounds, an even number of univalent atoms are always added at a time—two, four, or six atoms of chlorine, bromine, or hydrogen, to form compounds of the general formulæ  $C_6H_6X_2$ ,  $C_6H_6X_4$ , and  $C_6H_6X_6$ . In no instance are more than six such atoms added; hexamethylene, for example, the hexahydride of benzene,  $C_6H_6 \cdot H_6$  or  $C_6H_{12}$ , is the final reduction product. It is these products that have led to the view that the linking of the atoms in benzene and its derivatives must differ from that of the compounds hitherto considered.

<sup>1</sup> Cf. Chap. vii. p. III.

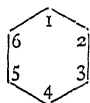
*The Substitution Products of Benzene; Isomerism amongst Aromatic Compounds.*—According to Kekulé's benzene theory, the six carbon atoms of benzene which form the *nucleus* of all aromatic compounds are linked together by alternate single and double bonds to form a closed chain or ring. Each carbon atom has under these conditions one valency unsaturated, and these are combined with hydrogen, in benzene, to form  $C_6H_6$  :—



Kekulé's Benzene formula.

That each hydrogen atom in benzene is connected with one carbon atom, as represented in this formula, has been conclusively proved by the number of substitution products that can be formed when one or two of the six hydrogen atoms are substituted by a univalent element or group. Kekulé pointed out that owing to the symmetrical relation of the six hydrogen atoms in his benzene formula only one monosubstitution product, such as monobrombenzene,  $C_6H_5Br$ , should exist, but that there should be three dibrombenzenes,  $C_6H_4Br_2$ . This prediction has been fully confirmed, by direct experiment, by Ladenburg and others, the process adopted being akin to that employed in proving the symmetry of the methane molecule.<sup>1</sup>

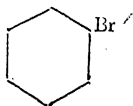
The isomeric relations of the aromatic compounds are most simply stated and studied by representing the benzene nucleus as a regular hexagon, the angles of which are numbered from 1 to 6 :—



Benzene Hexagon.

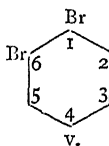
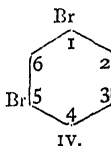
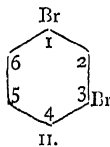
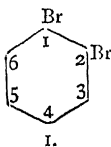
<sup>1</sup> Chap. ii. p. 23.

The symbols C and H are omitted for the sake of simplicity, and also the alternate double bonds between the carbon atoms. Monobrombenzene is written graphically thus:—



Monobrombenzene,  $C_6H_5.Br$ .

This represents benzene in which one atom of hydrogen is replaced by bromine. Since benzene has been proved to have a symmetrical structure, it does not matter which of the six hydrogen atoms is replaced by the one atom of bromine; the same product must result in all cases. When a second hydrogen atom is replaced, three, and only three, isomeric substances can be formed theoretically, and this again accords with the experimental results. Supposing the first substituent is at 1, the second bromine atom can occupy any of the positions 2 to 6, thus:—



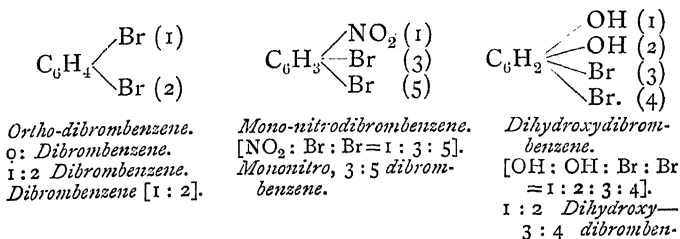
A little consideration will show that the formulæ I. and V. are identical, and also II. and IV.; in the former the bromine is attached to adjacent carbon atoms, and in the latter to carbon atoms separated by one carbon atom of the ring. In order to distinguish these three isomers by name, the prefixes *ortho*, *meta*, and *para*, introduced by



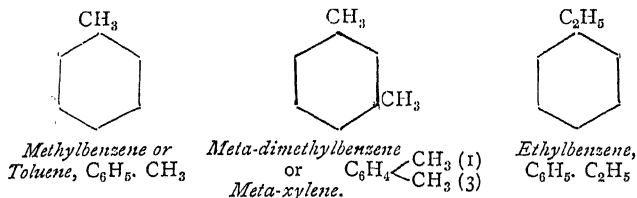
Körner<sup>1</sup> (1867), are employed. When these prefixes were first applied to aromatic compounds their structure was unknown, and hence the prefixes have no special genetic significance; at that time there was no idea of establishing any structural relationship between compounds to which the same prefixes applied. For instance, the substitution products obtained directly from aniline were originally not given any differentiating prefix, and the others were called "para" compounds; the discovery by Körner of a third isomeric disubstitution product of benzene led him subsequently to introduce the prefix "meta" to distinguish it from its two isomers, and at the same time he called the name "ortho"-compounds for the original, previously no prefix had been applied. Subsequently the structure of the compounds became known, and these prefixes were then used to denote the relative positions of the substituents in the benzene ring. Compounds in which the substituents are adjacent are now called *ortho-compounds*, and are said to have their substituents in the ortho or 1:2 position (Formulæ I. and V.), the 1:3 compounds are the *meta* (Formulæ II. and IV.) and the 1:4 compounds the *para* (Formula III.). These positions, it is to be remembered, are purely relative; the numbering of the hexagon can, of course, begin at any of the angles, and therefore 1:2 is the same as 6:1 or 2:3, etc.; 1:3 is equivalent to 2:4 or 4:6; and finally, 1:4, 2:5 and 3:6 are identical. When more than two atoms of hydrogen are replaced, and especially when the substituents are different, the conditions of position isomerism become more complex; thus, whilst there are six tribromobenzenes,  $C_6H_3Br_3$ , there are six mononitro-  
 $C_6H_5NO_2$

The nomenclature of the substitution products of benzene is based on the relative position of the substituents in the ring; the hexagon itself is not written, but simply figures indicating the relative position of the substituting atoms or groups. With di-substitution products, the prefixes ortho, meta, and para are used, or their initial letters *o*, *m*, and *p*. A few examples will illustrate this method, and may be useful for reference:—

<sup>1</sup> "Faits pour servir à la détermination du lieu chimique dans la série aromatique," *Jahresberichte*, 1867, p. 615.



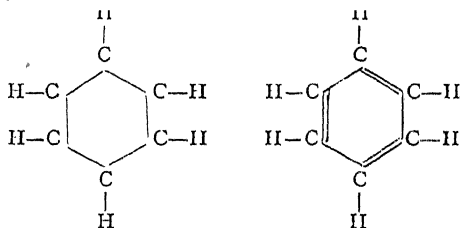
The homologues of benzene arise when one or more of the hydrogen atoms are replaced by a hydrocarbon radical such as methyl or ethyl:—



These substituting groups are called *side chains*; they do not form an essential part of the benzene ring, and are comparatively easily eliminated, leaving the benzene nucleus intact. Their presence gives rise to an additional isomeric relation, for their hydrogen atoms can be replaced as in the case of the paraffins. Thus, the first homologue of benzene, methylbenzene or *toluene*,  $\text{C}_6\text{H}_5.\text{CH}_3$ , forms four isomeric monobromoderivatives—namely, three monobromotoluenes,  $\text{C}_6\text{H}_4.\text{Br}.\text{CH}_3$ , as with any disubstitution product of benzene, and, in addition, a compound of the formula  $\text{C}_6\text{H}_5.\text{CH}_2\text{Br}$  called *benzyl bromide*, the univalent radical  $\text{C}_6\text{H}_5\text{CH}_2$ , being known as *benzyl*. Such side-chain substitution products differ from those in which a hydrogen atom in the benzene ring is replaced both in their methods of preparation and properties.

*The Structure of Benzene.*—The formula proposed by Kekulé for benzene (p. 66), in which the carbon atoms are united by alternate single and double bonds to form a closed ring, is not entirely satisfactory. The fact that the carbon atoms are disposed in the form of a closed chain

is amply proved by the conditions of isomerism amongst aromatic compounds, the relation of benzene to its homologues, and the marked stability of the benzene nucleus. It is further supported by numerous syntheses of benzene derivatives from open-chain compounds, and is accepted by all chemists as the basis for the structure of benzene. But the assumption that benzene contains unsaturated ethylene linkings, as represented in the Kekulé formula, is contrary to many of its properties, and hence a number of alternative formulæ have been put forward. Any structural formula for benzene must, of necessity, fulfil the conditions which have led to the acceptance of the regular hexagon, as the partial representation of the constitution of the hydrocarbon. On examining the hexagon formula for benzene, it is seen that three of the four affinities of each carbon atom are satisfactorily accounted for; the difficulty is to account for the fourth affinity. Although endless suggestions have been made, more or less supported by experiment, there is at present no formula for benzene which fully expresses its properties and the isomeric relations of its derivatives. A sketch of the merits of the most important of the proposed formulæ may serve to indicate the difficulties of the problem and the methods that have been employed in attacking it.<sup>1</sup>

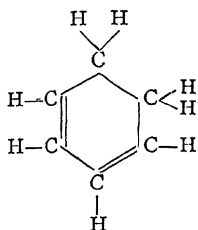


*Simple hexagon formula for benzene. Kekulé's benzene formula.*

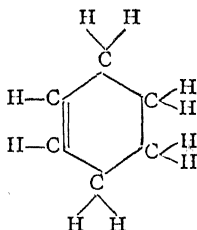
A comparison of the simple hexagon formula with the structural formula proposed by Kekulé shows how this fourth carbon affinity is disposed in the latter—viz., in the formation of three double bonds in the molecule. The

<sup>1</sup> For a fuller account of this subject see "Die Benzoltheorie" by Marckwald, *Sammlung chem. und chem.-technischer Vorträge*, 1897, published by Enke, Stuttgart.

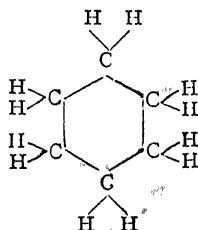
formation of the addition products of benzene is easily represented on this formula. In these compounds it will be remembered that addition products containing two, four, or six atoms of hydrogen or chlorine, but never more than six atoms, can be formed. If the alternate double bonds between the carbon atoms are successively attacked, say by hydrogen, such addition products would result, and three hydrides of benzene would be formed having the following formulæ:—



*Dihydrobenzene,*  
 $C_6H_6.H_2$



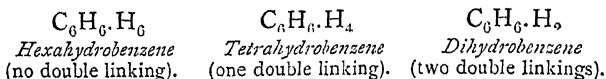
*Tetrahydrobenzene*  
 $C_6H_6.H_4$



*Hexahydrobenzene*  
 $C_6H_6.H_6$   
(*Hexamethylene*).

Similar addition products are, of course, obtainable from the derivatives of benzene, and the methods of formation and properties of such compounds have been thoroughly investigated, especially by von Baeyer, who made an exhaustive study of the addition compounds obtained from the three benzene dicarboxylic acids (phthalic acids); his conclusions apply to all similarly constituted compounds, such as the above simple hydrides. When two atoms of hydrogen are added to a benzenoid compound, the resulting substance possesses all the characteristics of a compound containing two double bonds; it readily takes up four atoms of bromine, or two molecules of hydrobromic acid to form a saturated cyclic compound, and is attacked by oxidising agents. Similarly, when four atoms of hydrogen are added, the resulting tetrahydride resembles ethylene or any similar compound containing one double bond, in its chemical behaviour, and finally a completely reduced benzene ring like the hexahydride, hexamethylene, behaves like a saturated cyclic (alicyclic) compound, and is distinctly

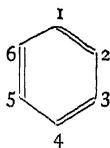
aliphatic in character. These conclusions may be summarised as follows:—



It would therefore be expected that benzene itself should behave as if it contained three double linkings, as represented in Kekulé's formula. As was mentioned above, benzene can under certain conditions be induced to take up chlorine, etc., with the formation of addition compounds, but these compounds are formed only with difficulty, whereas dihydrobenzene and tetrahydrobenzene combine with halogens with great avidity, acting precisely like unsaturated aliphatic compounds in this respect.

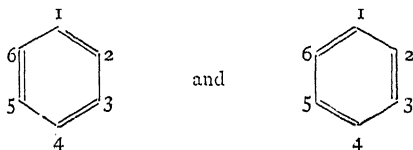
Further, the halogen acids such as hydrobromic acid are entirely without action upon benzene, although they readily form addition compounds with dihydrobenzene and with tetrahydrobenzene as with unsaturated aliphatic compounds. Whilst, therefore, the one or two double bonds in the reduction products of benzene represent a condition of combination analogous to that in ethylene, the three double bonds in benzene itself, as represented in Kekulé's formula, in no way serve to interpret the properties of the simple hydrocarbon. The function of the double bonds in benzene must accordingly be essentially different from that in its reduction products, or in ethylene and its homologues.

There is a further objection to the formula. The positions 1:2 and 1:6 are not identical:—

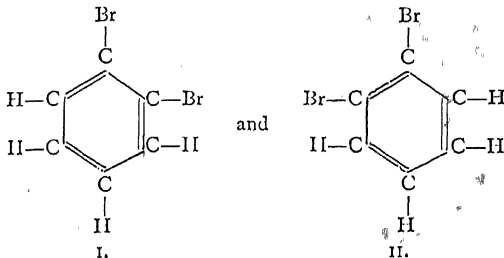


The carbon atoms 1 and 2 are connected by a double bond, whilst 1 and 6 are connected by a single bond. Hence 1.2 dibrombenzene should, for instance, differ from 1.6 dibrombenzene; there should therefore be four di-substitution products of benzene instead of three. This argument

was brought against Kekulé's formula at an early date, and he met it by an extension of his original idea expressed in what is generally known as Kekulé's *oscillation formula* for benzene, in which it was assumed that the benzene molecule oscillated between the following two formulæ:—

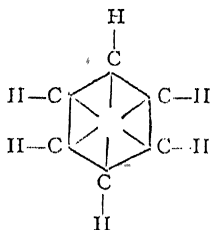


With this assumption the difference between the two positions 1:2 and 1:6 vanishes, and the two formulæ I. and II. for a dibrombenzene:—



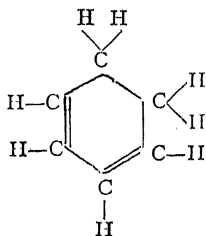
represent really one and the same ortho-compound. This interpretation will be more appropriately considered in connection with dynamic isomerism (Chapter XIV.).

The relation of benzene to its reduction products led von Baeyer (1888) to a different conception of the structure of the benzene molecule, expressed graphically by his *centric formula*, which had been previously suggested by Armstrong (1887):—



Centric formula for benzene.

In this formula one valency of each carbon atom is supposed to be directed towards the centre of the ring, and the six valencies are assumed to neutralise each other, owing to the symmetrical position of the carbon atoms. These valencies are, according to this representation, only called into evidence when the stability of the molecule is changed by the formation of addition products. When two atoms of hydrogen, for instance, are added to form dihydrobenzene, the equilibrium of the molecule is disturbed, and the liberated affinities of the remaining four carbon atoms unite with each other with the formation of two double bonds:—



Dihydrobenzene,  $C_6H_8$ ,  $H_{12}$ .

In contradistinction to Kekulé's formula, the reduction of benzene to dihydrobenzene involves the *formation* of two double bonds. The subsequent addition of two or four more univalent atoms is in every way analogous to the saturation or partial saturation of any other unsaturated compound, and this analogy is completely in accord with the chemical properties of these addition compounds as already stated. Several other formulæ have been suggested, and von Baeyer attempted to decide between the most plausible of them by studying the position of the added hydrogen atoms in the reduction products of certain benzene derivatives. In Kekulé's formula, for instance, these must necessarily attach themselves to adjacent carbon atoms. But this method, which at first appeared to be a crucial means of deciding the structure of benzene, and which really led von Baeyer to his centric formula, has proved unsatisfactory on account of intramolecular changes that were subsequently found to occur in the reactions involved. The present knowledge of the structure of benzene

has been summarised in the following words<sup>1</sup>:—"The molecule of benzene consists of six CH groups, which are symmetrically united to form a ring by the three carbon valencies of each group, 18 valencies in all. Since 12 valencies suffice to unite the six groups, an excess of six valencies remains, which effects a more intimate linking of the six groups of the ring, owing to a different condition of combination to that which ordinarily occurs amongst other compounds. When, in the formation of addition products, these excess valencies are called into play, in three successive pairs, in order to link the added atoms to the nucleus, such a rearrangement of the original condition of combination in the ring occurs that the single valencies are used up in pairs with the formation of ordinary double or single bonds." The centric formula gives the clearest expression of this statement, but it is indefinite as to the nature of "the more intimate linking" effected by the six excess or *potential* valencies of the benzene molecule.

Very many hypothetical suggestions have been made as to the nature of the potential valencies,<sup>2</sup> but so far no formula has been proposed which is in all respects satisfactory for benzene and applicable to all its derivatives. It is by no means necessary, however, to conclude that the conditions of combination in the benzene ring are always the same. The potential valencies may exert their influence on neighbouring carbon atoms in some benzenoid compounds as represented by Kekulé's formula, or mutually upon each other according to the centric formula in other compounds, and there is some experimental evidence in favour of this view.<sup>3</sup>

In his original memoir on the structure of benzene Kekulé says, referring to different possible formulæ for benzene—"A problem of this kind might at first sight appear quite insoluble, but I nevertheless believe that experiment will furnish a solution." This was in 1865. Despite the unlimited field of inquiry opened out by Kekulé's brilliant conception of the structure of benzene,

<sup>1</sup> Victor Meyer and Jacobsen, *Lehrbuch der organischen Chemie*, vol. ii. p. 60.

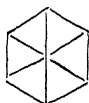
<sup>2</sup> Cf. Thiele, *Annalen*, 1899, cccxi. 87; Knoevenagel, *Berichte*, 1903, xxxvi. 2803.

<sup>3</sup> Cf. Chap. xiv. p. 396.

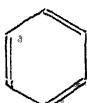


and since investigated with exceptional ardour, the experimental solution of the problem has nevertheless baffled the best efforts of chemists for forty years.

*The Bearing of the Physical Properties of Benzene and of its Derivatives on the Structure of the Benzene Ring.*—In studying the thermochemical relations of saturated and unsaturated hydrocarbons, it was observed that the constitutional differences in the structure of these compounds is represented by a corresponding difference in their heats of formation. There are many other physical properties of compounds which depend not only upon the number and kind of atoms present in the molecule, but also upon the way in which they are linked together.<sup>1</sup> Such properties are termed *constitutive*, in contradistinction to *additive* properties, which depend only upon the number of atoms of each element present, and are independent of their method of combination. Until comparatively recently many chemists looked hopefully to the physical constants of benzene as a means of deciding the structure of the molecule, by furnishing a definite proof as to whether the six carbon atoms in the ring are united together by three single and three double bonds, as in the Kekulé formula, or by nine single bonds, as in several predecessors of the centric formula, and in a modified way in the centric formula itself. This difference is shown graphically by the following outline formulæ:—



I. Diagonal formula.  
9 single bonds.



II. Kekulé formula.  
3 single and 3 double bonds.

The heat of combustion, the molecular volume, and the molecular refraction<sup>2</sup> have each a different value for a double as compared with a single bond between two carbon atoms, and these differences have been determined amongst aliphatic compounds. But the attempts made to apply the constants for these conditions of linking to benzene are of very doubtful value, because there is ample chemical evidence, as already shown, to prove that the potential

<sup>1</sup> Cf. Chap. xiv. p. 380.

<sup>2</sup> *Ibid.*, p. 381.

valencies of benzene are entirely different from those of ethylene and its homologues. Apart from this, the conclusions that have been drawn are by no means concordant; thus, the heat of combustion and the molecular volume point to nine single bonds, whilst the molecular refraction accords with three single and three double bonds.

Whilst, however, such evidence from physical constants is quite outweighed by chemical considerations in respect to the structure of benzene itself, it should be possible to elucidate the relation of benzene and its derivatives to their reduction products by the study of their constitutive physical properties, and thus indirectly to throw light on the structure of the hydrocarbon. According to the Kekulé formula, the addition of two hydrogen atoms to benzene should be analogous to the conversion of ethylene into ethane, and should therefore be represented by an equivalent quantitative value in any constitutive physical property; the further addition of two or four atoms of hydrogen should similarly involve a corresponding change. The two latter additions should show the same quantitative relations in the case of the centric formula; but the first change, from benzene to its dihydride, should be different, on account of the change in the condition of combination of the carbon atoms that accompanies this first addition. The evidence of the physical constants on this point is, however, not concordant. The molecular refraction and the molecular volume favour the Kekulé formula, whilst careful experiments by Stohmann<sup>1</sup> on the heat of combustion of the reduction products of aromatic compounds have led him to the conclusion that the thermal value of the addition of hydrogen to the benzene ring is entirely different in the first stage from what it is in the second and third stages, and that in both these latter stages it is in agreement with the thermal values for the addition of hydrogen to ordinary double-bond compounds in the aliphatic series. This is completely in accord with the present view of the structure of benzene as expressed by the centric formula, but the fact that other constitutive physical properties lead to a different conclusion still awaits explanation.

<sup>1</sup> *J. Chem. Soc. Abstracts*, 1891, ix. 376; also Baeyer, *Annalen*, 1894, cclxxviii. 115; and Brühl, *J. prakt. Chem.*, 1894, xlix. 260.

*The Orientation of Aromatic Compounds.*—Although a complete explanation of the structure of benzene is still wanting, the simple hexagon, the basis of all the proposed formulæ, supplies a sufficiently satisfactory working hypothesis for the study of the isomeric relations of benzene derivatives. In formulating these derivatives the fourth affinity of each carbon atom in the ring is disregarded.

The number of possible isomers with two or more substituents, like or unlike, that can be derived from benzene and its homologues is indicated theoretically by the hexagon formula, and so far experiment has fully substantiated these indications.

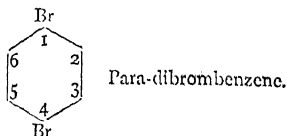
But it is necessary in addition to be able to ascertain and assign the relative position of these substituting atoms or groups in benzenoid compounds. This assigning of the position of the substituents in the benzene ring is known as the *orientation* of aromatic compounds. It does not, of course, concern monosubstitution products, because all the hydrogen atoms of benzene are equivalent. The methods employed for arriving at the orientation were for a long time unreliable, and changes were continually being made which led to much confusion and inconsistency. These older methods were based on an incomplete understanding of the proper relation of substitution products to one another, and it was only when this relationship was thoroughly grasped that a true basis for orientation was obtained. When the orientation of a few characteristic substitution products was once satisfactorily established, that of other benzene derivatives became a comparatively easy problem, for by converting the latter into or obtaining them from the former, the position of their substituents could be directly inferred. This principle is still adhered to, with the restriction that only such reactions are relied upon as are likely to be free from possible molecular rearrangements. Although in the great majority of instances substituents in the benzene ring replace one another without intramolecular rearrangement, there are many instances in which a change does take place in the position of the substituents, especially when high temperatures are necessary to effect a reaction, or when certain reagents of a very active character are used; fusion with the hydroxides of the alkali metals, for instance, is a type

of such an action, and therefore decompositions by these reagents are now avoided in deducing the orientation of compounds. Provided, however, that the reactions are carried out at a comparatively low temperature, and that the change is fairly complete, the conclusions as to the similar orientation of the compounds involved in the change are considered to hold good. Thus, for example, a certain dinitrobenzene,  $C_6H_4(NO_2)_2$ , readily yields a diaminobenzene,  $C_6H_4(NH_2)_2$ , upon reduction, or a certain dimethylbenzene,  $C_6H_4(CH_3)_2$ , forms a dicarboxylic acid,  $C_6H_4(COOH)_2$ , on oxidation; the acid is therefore regarded as having its carboxyl groups in the same position in the benzene ring as were previously occupied by the two methyl groups, and similarly with the two substituting groups of the diamino- and dinitro-benzene.

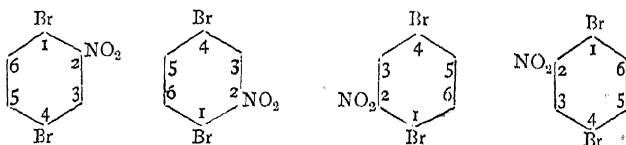
It remains, therefore, to establish the orientation of certain aromatic compounds which shall serve as a basis; from these that of all others can then be deduced. This has been satisfactorily accomplished in several ways, and that the conclusions are reliable is proved by the fact that the results obtained by the different methods are in complete accord. An outline of one method, that due to Körner (1874), will suffice.

There are three dibromobenzenes known; one is a liquid boiling at  $224^\circ$ , the second boils at  $220^\circ$ , and the third is a solid melting at  $87^\circ$ . By the action of nitric acid these form mono-nitrodibromobenzenes, one atom of hydrogen in the nucleus being replaced by the nitro-group  $NO_2$  in each case. These mono-nitrodibromobenzenes have the formula  $C_6H_3(NO_2)Br_2$ , and six different products in all arise from the three dibromobenzenes; this is the correct number of isomers for any tri-substitution product of benzene containing two different substituents according to the hexagon formula. Of these six isomers, as Körner pointed out, only two can be derived from a compound, having its two bromine atoms in the ortho-position, three from the meta-dibromobenzene, and one from the para-compound. The liquid boiling at  $224^\circ$  was found to give two of the six mono-nitrodibromobenzenes, that boiling at  $220^\circ$  gave three, and the solid isomer only one; they are therefore the ortho-meta- and para-compounds respectively. A glance at the possible substitution products that could be formed from

para-dibrombenzene by replacing a hydrogen atom by the nitro-group, as illustrated by the hexagon formula, will render this method of arriving at the orientation of aromatic compounds clear.



The hydrogen atoms at 2, 3, 5, or 6 can be replaced by another substituent, such as the nitro-group, but the resulting compound, as can be seen from the following formulæ, will be the same in each case owing to the symmetry of the benzene ring:—



The order Br:NO<sub>2</sub>:Br is 1:2:4 in each case; the relative position of the three substituents is identical, as indicated by the different order in which the angles of the hexagon are numbered above. Therefore, para-dibrombenzene can only give one mono-nitrodibrombenzene, or, in other words, that dibrombenzene, which gives only one mononitro-derivative, must be the para-compound. The derivation of the orientation of the ortho- and meta-compounds follows on exactly analogous lines. The method can also be reversed, and this has been done in the case of the three diaminobenzenes, the orientation of which has been deduced by Griess from their respective relations to the six diaminobenzoic acids. The dibrom- and diamino-benzenes can be converted into many other di-substitution products or obtained therefrom, so that there is no lack of compounds of known orientation on which to base that of any newly-discovered substances. The relation of the di-substitution products of benzene to the tri-substitution products furnishes also the means for determining the orientation of the latter.

## CHAPTER VI.

### THE MELTING POINT AND BOILING POINT OF ORGANIC COMPOUNDS.

*The Melting Point of Organic Compounds.*—The determination of the melting point—The relation of the melting point to the composition and structure of compounds.

*The Boiling Point of Organic Compounds.*—The determination of the boiling point—Distillation under reduced pressure—The relation of the boiling point to the composition and structure of compounds.

*Fractional Distillation.*—The fractional distillation of mutually miscible liquids—The distillation of non-miscible liquids: distillation by steam.

THE nature of organic compounds renders it necessary to apply very different methods for their identification from those used in inorganic chemistry. The identity of an inorganic compound may be established by a relatively simple and systematic scheme of qualitative analysis depending upon the reactions of the metals and acids. In organic chemistry such a general scheme of analysis is not practicable. It is a simple matter to detect the elements present in an organic compound, but since the same elements occur in a vast number of different substances, much more than this is necessary for the identification of a compound. The majority of the reactions used in organic chemistry are of a general nature; they apply to whole classes of compounds such as acids, alcohols, etc., and, therefore, other means are necessary for the identification of the individual members of each class. These consist in the determination of certain physical properties, of which the melting point and boiling point are by far the most important.

## THE MELTING POINT OF ORGANIC COMPOUNDS.

Almost all crystalline organic compounds liquefy at a definite temperature when heated; this temperature is taken as the melting point of the solid. A few substances sublime without melting, others decompose; the temperature of decomposition is frequently fairly well marked but seldom so definite as the melting point. The melting point provides an easy and ready means for the identification of compounds; in addition, a constant and sharply-defined melting point is almost always a sign of purity. Impure products do not melt sharply, but usually over an interval of several degrees, whilst compounds, sufficiently pure for all ordinary laboratory work, are completely melted within half a degree or at most within one degree of their melting point. Impurities generally lower the melting point, and a rise in the latter after recrystallisation indicates increased purity; a constant melting point after recrystallisation is taken as a sign of purification, and is used as a gauge of the purity of new compounds.

*The Determination of the Melting Point.*—To determine the melting point of a substance a small quantity is heated in a suitable bath, and the temperature at which it melts observed by means of an accurate thermometer. The form of apparatus commonly employed is shown in Fig. 2. The bulb (A) has a capacity of about 100 c.c., and is filled two-thirds full of the liquid which serves as the bath; strong sulphuric acid is generally used. The tube of the bulb-tube is provided with a cork (B), in which the thermometer (T) is fitted; a small slit is cut in the side of the cork to allow for the expansion of the air in the tube during the heating. The substance is first dried, ground up to a fine powder, and then quite a small quantity introduced into a thin capillary tube, the form and actual size of which are shown in Fig. 3. This tube is then fastened to the stem of the thermometer by means of a piece of platinum wire or ring of rubber tubing in such a position that the substance is

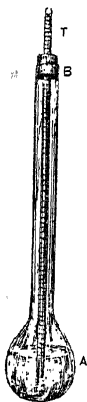


FIG 2



FIG 3

level with the centre of the bulb of the thermometer. The bath is then gently heated until the substance melts and falls together, when the temperature is noted. As the melting point is approached, the heating should be proceeded with very gradually. A check determination is always advisable, and for accurate work the temperature should be corrected for the exposed portion of the mercury column.

*The Relation of the Melting Point to the Composition and Structure of Compounds.*<sup>1</sup>—Certain regularities have been observed in the melting points of compounds, especially amongst isomeric substances and members of the same homologous series.

In the case of isomeric compounds, that having the most symmetrical structure has the highest melting point. Thus, the symmetrical ethylene derivatives have all a higher melting point than the isomeric ethylidene compounds:—



Succinic acid, m.p. 180°.    Isosuccinic acid, m.p. 129°.

Amongst aromatic compounds, the para-compounds, which are the most symmetrical, have the highest melting point.

In several homologous series of organic acids an alternate rise and fall in the melting point accompanies an increase in the molecular weight, the acid with an even number of carbon atoms melting higher than the next higher homologue with an odd number, but the rise in the odd and even series respectively is similar in character. This peculiarity is well shown amongst the higher fatty acids:—

Palmitic acid,	m.p. 62°
Margaric acid,	60°
Stearic acid, $\text{C}_{18}\text{H}_{36}\text{O}_2$ .	69°
Nondecylic acid, $\text{C}_{19}\text{H}_{38}\text{O}_2$ .	66°.5

Other relations between the melting point and structure of compounds are for the most part irregular in character

<sup>1</sup> Cf, *Siede und Schmelzpunkt; ihre Theorie und praktische Verwertung*, Nernst and Hesse, 1893.



beyond a few broad generalities, of which the following are typical. The substitution of hydroxyl for hydrogen is accompanied by a rise in the melting point, as is also the case when a carboxyl group is introduced, whilst when the latter is converted into its methyl ester, the melting point is lowered—*e.g.* :—

Benzene	-	-	$C_6H_6$	m.p. $5^{\circ}.4$
Hydroxy-benzene (Phenol)	-	-	$C_6H_5OH$	„ $43^{\circ}$
Benzoic acid	-	-	$C_6H_5COOH$	„ $121^{\circ}.4$
<hr/>				
Oxalic acid	-	-	$COOH$	„ $189^{\circ}$
			$ $ $COOH$	
Dimethyl-oxalate	-	-	$CO.OCH_3$	„ $54^{\circ}$
			$ $ $CO.OCH_3$	
<hr/>				
Naphthalene	-	-	$C_{10}H_8$	m.p. $80^{\circ}$
$\beta$ -Naphthol	-	-	$C_{10}H_7OH$	„ $122^{\circ}$
$\beta$ -Naphthyl methyl ether	-	-	$C_{10}H_7OCH_3$	„ $70^{\circ}$
$\beta$ -Naphthoic acid	-	-	$C_{10}H_7COOH$	„ $182$
Methyl $\beta$ -naphthoate	-	-	$C_{10}H_7COOCH_3$	„ $77^{\circ}$

Such regularities in the melting points of allied compounds, of which the above are simple examples, have an important practical value, since they furnish the data for an approximate precalculation of the melting point of a new compound. The calculated value should, of course, approach that actually observed; if it does not, the synthetical reaction employed has probably proceeded abnormally or some group present in the original compound has been unexpectedly eliminated in the preparation of the new derivative.

#### THE BOILING POINT OF ORGANIC COMPOUNDS.

A constant boiling point, like a constant melting point, is an indication of the purity of a compound, and has a similar value as a means of identification. Impurities may either raise or lower the boiling point according to their character, but with a certain limited number of exceptions mixtures of organic compounds boil over a

considerable range of temperature, between the boiling points of their constituents.

The temperature at which a substance boils is dependent upon the pressure to which its vapour is subjected, and, therefore, the boiling point, as usually observed, varies with the atmospheric pressure. All liquids exert a certain gas pressure at all temperatures, due to the vapour of the liquid; this pressure is known as the *vapour pressure* of the liquid. It increases with a rise of temperature, and when it just exceeds the atmospheric pressure the liquid boils. In determining a boiling point it is therefore necessary to observe the height of the barometer, and for accurate comparisons to correct the boiling point to the standard atmospheric pressure of 760 millimetres of mercury. An approximate general formula for this correction is to be found in any text-book on physics; increased pressure raises the boiling point and vice versa.<sup>1</sup> The influence of a decreased pressure on the boiling point is shown in the following table:—

Substance.	Boiling Point at 760 mm.	Boiling Point at 12 mm.	Difference.
Water - -	100°	14°.1	85°.9
Acetic acid - -	118°.7	19°.4	99°.3
Aniline - -	182°	72°.7	109°.3
Naphthalene - -	218°	88°.5	129°.5
Acetamide - -	222°	109°	113°
Glycerol - -	291°.3	169°.6	121°.7
Acetanilide - -	295°	166°.6	128°.4

Many compounds, such as the higher alcohols and esters, are decomposed when distilled at the ordinary pressure, but the lowering of the boiling point by decreasing the pressure allows of their being distilled without decomposition. Distillation under reduced pressure is, therefore, often made use of for the isolation and purification of such compounds. As shown in the last column of the table, the difference in the boiling point at 12 mm. and at 760 mm. increases with an increase in

<sup>1</sup> Cf, *Siedetemperatur und Druck in ihren Wechselbeziehungen*, Kahlbaum, 1885.

the boiling point, so that difficultly volatile substances gain more than a proportionate advantage when distilled under reduced pressure.

*The Determination of the Boiling Point.*—The distillation of liquids, for the determination of their boiling point or for their purification, is conducted in fractionating flasks (Fig. 4).

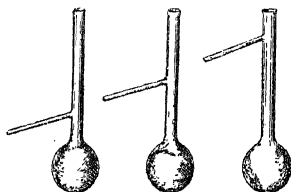


FIG 4

These flasks differ in size according to the quantity of liquid to be distilled, and also in the position of the exit tube, as shown. A thermometer is fitted into the flask by means of a bored cork, and for ordinary distil-

lations the bulb of the thermometer is placed just below the exit tube of the flask (Fig. 5). In this position a portion of the stem of the thermometer registering the temperature will usually be outside the flask, and, therefore, at the temperature of the surrounding air instead of at that of the vapour of the substance.

A correction must be made in such cases for this exposed portion of the mercury column, but for accurate boiling point determinations this correction is usually obviated by employing short thermometers, which allow of the stem being completely surrounded by vapour. For substances of high boiling point a simple glass tube will suffice for the condensation of the vapour evolved in the determination (Fig. 6), but for more volatile substances a jacketed tube is necessary (Fig. 7). This

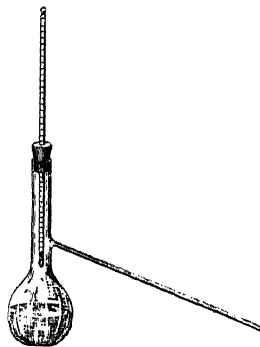
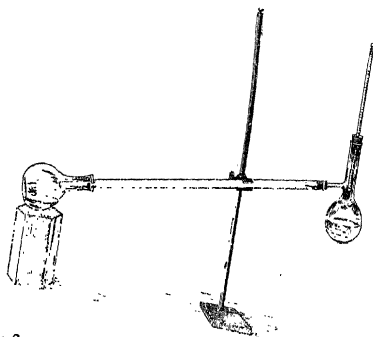


FIG 5

invaluable piece of laboratory apparatus, in which inner glass tube is cooled by a current of water run through a wider glass tube fixed outside it, is commonly known as a *Liebig's condenser*. As a matter of fact, it was originally

THE BOILING POINT OF ORGANIC COMPOUNDS. 87  
designed by Weigel in 1771, and Liebig himself made no  
claim to the invention of the apparatus.<sup>†</sup>



Having fitted the thermometer in the fractionating flask  
and attached the condenser, all that remains for the

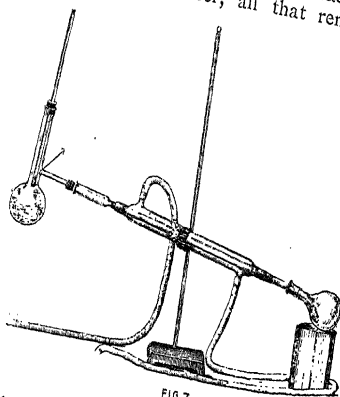


FIG. 7

determination of the boiling point is to heat the liquid.  
Liquids boiling below  $80^{\circ}$  are heated on a water-bath

<sup>†</sup> Kahlbaum, *Berichte*, 1896, xxix, 69,

(Fig. 14,  
boilin  
avoid

over a small luminous flame, higher  
e fre bunsen-burner. To

porous tile, which have  
allowed to cool, are placed i  
soon as the substance begi  
thermometer rises rapidly  
liquid, and in the case of a  
at the boiling point until  
has distilled over. In  
distillation any impurities of lower boiling point distil over  
first; as soon as t temperature becomes constant, a fresh  
for that originally placed at the end  
, and the distillate collected as long

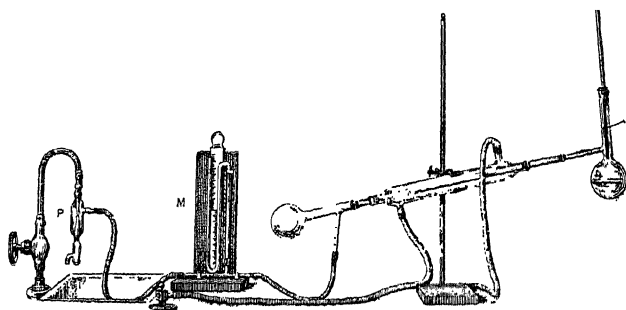


FIG 8.

as the liquid distils at this constant temperature. It should be observed, however, that unless the boiling points of the liquids lie far apart, a very imperfect separation is effected by a single distillation, as the two liquids volatilise simultaneously to a great extent. Ordinary laboratory preparations are sufficiently pure to distil within  $1^{\circ}$  of temperature, and certain commercial products, such as benzene and toluene, distilling within this limit are now manufactured.

*Distillation under reduced pressure.*—The apparatus employed for the distillation of substances under reduced pressure is exactly similar to that described, with the

addition of some suitable means for evacuating the fractionating flask, condenser, and receiver. These must be joined by air-tight connections, either of cork or rubber; the partial vacuum required is usually obtained by means of a water-pump (P), and in order to control and register the pressure, a manometer (M) is inserted between the pump and the receiver. This arrangement is shown in Fig. 8.

A special form of receiver for vacuum distillation is shown in Fig. 9, the advantage of which is that the distillate can be collected in a series of fractions without disturbing the vacuum; a metal rod (A), fixed in the stopper of the receiver, rotates the tubes in the wooden carrier (B), so that they can be brought opposite the end of the condenser tube (C) in succession. The tube D communicates *via* the manometer to the pump.

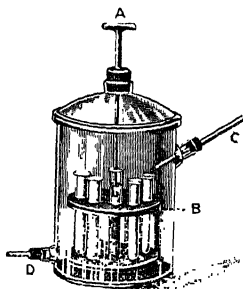


FIG. 9

In modern research-work, the water-pump is being largely superseded by various forms of piston pumps, working in oil, which reduce the pressure to a much lower point than is possible with the form of pump described above.

Special care is required in distilling substances under reduced pressure, owing to the liability of the heated liquid to bump or to froth over, and difficulty is sometimes experienced in maintaining a constant vacuum; otherwise, the identification and purification of compounds by this method of distillation is quite as readily carried out as when the boiling point is ascertained under the ordinary pressure.

*The Relation of the Boiling Point to the Composition and Structure of Compounds.*—Since the boiling point of all substances that distil without decomposition is always observed for the sake of their identification, ample data are available for the study of any connection between the composition and boiling points of compounds. The first numerical relations in this respect were pointed out by

Kopp (1842), who stated that "equal differences in the composition of organic compounds correspond to equal differences in their boiling points." Thus, in the homologous series of alcohols, acids, and esters he stated that there is a difference of  $18^\circ$  in passing from one member of the series to the next; this increment corresponds to the replacement of a hydrogen atom by  $\text{CH}_3$ , that is, to a difference of  $\text{CH}_2$  in the molecular formula. Subsequent determinations showed that this difference is not quite constant, but that it decreases as the molecular weight increases; also, that the values vary somewhat in different homologous series. Moreover, as a result of further study,<sup>1</sup> it has been pointed out that reliable comparisons can only be made with substances of special purity, and which are in no way abnormal in respect to their physical properties. The compounds from which Kopp drew his generalisations, especially alcohols and acids, are now known to be abnormal in regard to physical properties in many respects, so that his conclusions are no longer tenable, but accurate determinations of the boiling point of compounds that behave normally, such as the hydrocarbons and their halogen derivatives, show that the relation of this property to their composition is sufficiently well defined to be expressed by a simple formula. Of the several formulæ that have been suggested to express this relation, that of Young<sup>2</sup> appears to be the most accurate and most general. The difference ( $\Delta$ ) between the boiling point in absolute degrees ( $T$ ) of the compound and that of its next higher homologue is represented by the equation:—

$$\Delta = \frac{144.86}{T^{0.0148} \sqrt{T}}$$

In the following table the boiling points of the first eight normal paraffin hydrocarbons and those of their corresponding chlorides, bromides, and alcohols are given, together with the increment in boiling point ( $\Delta$ ) between successive members in each homologous series:—

<sup>1</sup> Young, *Phil. Mag.*, Series VI., 1905, ix. 1.

<sup>2</sup> *Loc. cit.*

THE BOILING POINT OF ORGANIC COMPOUNDS.

Hydrocarbon.	Boiling Point.	$\Delta$	Chloride.	Boiling Point.	$\Delta$	Bromide.	Boiling Point.	$\Delta$	Alcohol.	Boiling Point.	$\Delta$
$\text{CH}_4$	-164.7		$\text{CH}_3\text{Cl}$	-23.7		$\text{CH}_3\text{Br}$	4.5		$\text{CH}_3\text{OH}$	64.7	
$\text{C}_2\text{H}_6$	-93	71.7	$\text{C}_2\text{H}_5\text{Cl}$	+12.5	36.2	$\text{C}_2\text{H}_5\text{Br}$	38.4	33.9	$\text{C}_2\text{H}_5\text{OH}$	78.3	13.6
$\text{C}_3\text{H}_8$	-45	48	$\text{C}_3\text{H}_7\text{Cl}$	46	33.5	$\text{C}_3\text{H}_7\text{Br}$	70.8	32.4	$\text{C}_3\text{H}_7\text{OH}$	97.2	18.9
$\text{C}_4\text{H}_{10}$	+1	46	$\text{C}_4\text{H}_9\text{Cl}$	78	32.0	$\text{C}_4\text{H}_9\text{Br}$	101	30.2	$\text{C}_4\text{H}_9\text{OH}$	116.9	19.7
$\text{C}_5\text{H}_{12}$	36.3	35.3	$\text{C}_5\text{H}_{11}\text{Cl}$	106.6	28.6	$\text{C}_5\text{H}_{11}\text{Br}$	129.5	28.5	$\text{C}_5\text{H}_{11}\text{OH}$	138	21.1
$\text{C}_6\text{H}_{14}$	69	32.7	$\text{C}_6\text{H}_{13}\text{Cl}$	133	26.4	$\text{C}_6\text{H}_{13}\text{Br}$	156	26.5	$\text{C}_6\text{H}_{13}\text{OH}$	158	20.0
$\text{C}_7\text{H}_{16}$	98.4	29.4	$\text{C}_7\text{H}_{15}\text{Cl}$	160	27.0	$\text{C}_7\text{H}_{15}\text{Br}$	179	23.0	$\text{C}_7\text{H}_{15}\text{OH}$	179	18.0
$\text{C}_8\text{H}_{18}$	125.6	27.2	$\text{C}_8\text{H}_{17}\text{Cl}$	184	24.0	$\text{C}_8\text{H}_{17}\text{Br}$	201	22.0	$\text{C}_8\text{H}_{17}\text{OH}$	191	15.0



## MODERN ORGANIC CHEMISTRY.

The decrease in the increment in boiling point for an addition of  $\text{CH}_2$ , as the series is ascended, is clearly evident in each group of compounds; it will also be noticed that whilst the boiling points of the chlorides are higher than those of the corresponding hydrocarbons, the value for  $\Delta$  is lower, and that a corresponding relation obtains between the bromides and chlorides. The alcohols show the highest boiling points of the substances included in the table as far as the first six members, and the smallest value for  $\Delta$ ; this value is also less regular than in the other series.

From the consideration of a large number of data, Young concludes that the values of  $\Delta$  may be calculated by the above formula, with an error of generally less than  $1^\circ$ , for the majority of organic compounds which contain straight chains of three or more carbon atoms ( $\text{C}-\text{CH}_2-\text{C}$  groups), and which are not associated in the liquid state; this limitation includes the hydrocarbons, their halogen derivatives, ethers, aldehydes, ketones, nitro-compounds, and amines, whilst the majority of the alcohols and acids are excluded. In nearly all homologous series the lowest members, usually the first two, show an abnormal boiling point in relation to the rest of the series, the value for  $\Delta$  being less than that calculated by Young's formula.

The figures in the above table, in addition to establishing the relations amongst the boiling points in homologous series, also show the change in boiling point that occurs when the hydrogen of a hydrocarbon is replaced by chlorine, bromine, or hydroxyl. Many similar data are available for other groups of compounds, such as esters, acid chlorides, nitro-compounds, ketones, aldehydes, etc., and the approximately definite change in the boiling point that occurs on the introduction of one of these groups is a valuable practical guide as to the course of a synthetical reaction.

There are, however, important limitations to these relations which it is necessary to bear in mind. Kopp's original statement of the relation between the boiling point and the composition of compounds would lead to the conclusion that isomeric compounds should have the same boiling point; this he subsequently admitted was not the case, and all later comparisons show that marked differences and also considerable irregularities exist. For

instance, when a hydrogen atom in a hydrocarbon is replaced by the hydroxyl group to form an alcohol, the average rise in the boiling point is about  $100^{\circ}$ , but it varies according to the position taken by the substituting group. Other substituents show a similar behaviour, indicating clearly that the boiling point is determined by the structure, as well as by the composition, of a compound, or in other words, that it is partly constitutive in its character.

There are four alcohols corresponding to the two hydrocarbons of the formula  $C_4H_{10}$ , butane and isobutane. The alcohols have the empirical formula  $C_4H_9OH$ ; their structural formulæ and boiling points are tabulated below:—

		Boiling Point.
<i>Normal Butane</i> , $CH_3.CH_2.CH_2.CH_3$	- -	$+1^{\circ}$
1. Normal butyl alcohol,	$CH_3.CH_2.CH_2.CH_2OH$	$117^{\circ}$
2. Secondary butyl alcohol,	$CH_3.CH_2.CHOH.CH_3$	$100^{\circ}$
<i>Isobutane</i> ,	$\begin{array}{c} CH_3 \\ \diagdown \\ CH-CH_3 \\ \diagup \\ CH_3 \end{array}$	$-17^{\circ}$
3. Isobutyl alcohol,	$\begin{array}{c} CH_3 \\ \diagdown \\ CH-CH_2OH \\ \diagup \\ CH_3 \end{array}$	$108^{\circ}$
4. Tertiary butyl alcohol,	$\begin{array}{c} CH_3 \\ \diagdown \\ C(OH)-CH_3 \\ \diagup \\ CH_3 \end{array}$	$83^{\circ}$

A study of these figures illustrates the generality that primary alcohols (1 and 3) boil higher than secondary (2), and these higher than tertiary (4). This difference corresponds to an increased branching of the chain of carbon atoms, and, with few exceptions, the boiling point amongst isomeric compounds is always lower the more branched the chain.

A simple outcome of the study of the boiling points of compounds is its partially additive character, and consequently the fact that all substances of high molecular weight have a high boiling point. This is often a valuable and early factor in indicating the course of a reaction.

Aldehyde, for instance, which boils at  $21^{\circ}$ , is readily converted into a liquid boiling  $100^{\circ}$  higher ( $124^{\circ}$ ). This at once indicates a change involving more than one molecule of the original substance, and, by suitable means, it has been shown that three molecules unite together in the reaction.



### FRACTIONAL DISTILLATION.<sup>1</sup>

The separation of the constituents of a mixture of liquids by distillation is one of the most important processes employed both in the laboratory and on a manufacturing scale. In the laboratory, the essential object of this method of separation, known as *fractional distillation*, is the isolation of pure compounds from the mixture. In industrial operations mixtures such as petroleum, the products of the fermentation industries and coal tar are thus separated into marketable products, some of which, such as the light oils of coal tar, are further fractionated into pure hydrocarbons. The behaviour of mixtures of liquids when boiled is different according as the liquids themselves are mutually miscible or not. The distillation of both miscible and of non-miscible liquids has each important practical applications; the conditions under which the distillation proceeds may be very complex in the former case, less so in the latter.

*The Fractional Distillation of mutually miscible Liquids.*—The separation of miscible liquids, which differ widely in their boiling points, is usually easily effected. A solution of aniline in ether, for instance, when distilled from a water-bath leaves the aniline completely behind, whilst the ether distils over; ether boils at  $35^{\circ}$  and aniline at  $184^{\circ}$ , and, therefore, there is a good margin for their separation. Ether, alcohol, and benzene are commonly used as solvents, in the extraction of organic compounds; they are all low boiling compounds (alcohol boils at  $78^{\circ}.3$  and benzene at  $80^{\circ}.2$ ), and this method of distilling off the solvent from the water-bath is a common laboratory operation.

But when the boiling points of the liquids in the mixture are nearer to each other the separation is far less complete

<sup>1</sup> A full account of the methods, results, and theory of fractional distillation is given in Professor Sydney Young's work, *Fractional Distillation*, 1903.

than might be anticipated. A gradual rise in the boiling point is to be observed as the distillation proceeds, which is accompanied by a corresponding change in the composition of the distillate, but at no stage during the distillation is there a constant boiling point or a pure distillate when the ordinary form of distillation apparatus, described above, is used. As an illustration of the incomplete nature of the separation of a mixture, the following results of distilling a mixture of ethyl alcohol B.P.  $78^{\circ}.3$ , and amyl alcohol B.P.  $138^{\circ}$ , are typical. One hundred grams of each alcohol were taken and separate fractions collected at intervals of  $10^{\circ}$ , which were subsequently analysed; four grams of pure amyl alcohol were left in the flask after the distillation:—

Boiling Point.	$80^{\circ}\text{--}90^{\circ}$	$90^{\circ}\text{--}100^{\circ}$	$100^{\circ}\text{--}110^{\circ}$	$110^{\circ}\text{--}120^{\circ}$	$120^{\circ}\text{--}130^{\circ}$	$130^{\circ}\text{--}138^{\circ}$
Weight of fraction	47	45	25	14	18	47
Ethyl alcohol, per cent . . .	88.1	82	61.5	52.1	18.4	1.7
Amyl alcohol, per cent . . .	11.9	18	38.5	47.9	81.6	98.3

By refractionating each fraction and uniting the corresponding distillates in each case a further separation can be effected, and by a continuation of this process pure products can be obtained; but this method of procedure involves great loss of material. To facilitate the separation, various forms of apparatus have been contrived, which consist of additions to the portion of the distillation flask between the bulb and the exit tube for the escaping vapours. These effect the condensation of the less volatile vapours, whilst the more volatile are allowed to escape and to pass over to the condenser. The most useful of the many forms of these *still-heads* or *dephlegmators* are shown in Fig. 10; they are attached to an ordinary flask by means of a bored cork, and are provided with an exit tube corresponding to that of an ordinary distillation flask.

With a plain vertical still-head, such as that of an ordinary fractionating flask, the evolved vapours escape practically without coming into contact with any of the condensed

liquid that forms in the still-head; it is for this reason that the separation is very incomplete. In the modified still-heads both of Hempel and Young, the efficiency of the apparatus is increased by promoting a much better admixture of the ascending vapour, owing to cross-currents and eddies, and by retarding the downflow of the condensed vapours. The Hempel still-head is simply a wide, glass tube packed with glass beads, to which a narrower tube, with an attached exit tube, is fitted. It is, therefore, very easily constructed, but since the beads retain a considerable

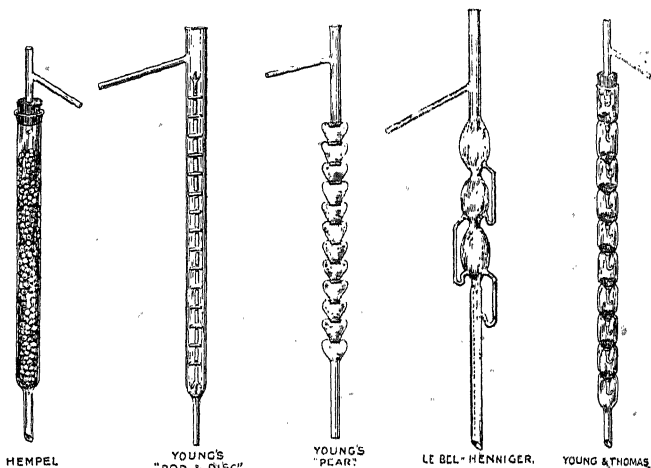


FIG. 10.

proportion of the mixture in the form of condensed liquid, it is unsuitable for the distillation of small quantities of material. Both the "rod and disc" and the "pear" still-head are so constructed as to cause a marked retardation of the condensed liquid in its flow from the still-head down to the distilling flask, and it is thus able to exert its fractionating effect on the ascending vapour. The "rod and disc" form can be advantageously used in the distillation of small quantities of liquid, whilst the "pear" still-head is specially recommended for the distillation of liquids of high boiling point.

The still-heads of Le Bel-Henniger, and Young and Thomas involve a somewhat different principle. The return flow of the condensed liquid is obstructed so as to cause it to collect in pools, through which the ascending vapours have to pass. A very complete contact between vapour and liquid is thus effected. Such forms of still-head are classed as *dephlegmators*. The Le Bel-Henniger dephlegmator consists of three or more bulbs, connected on alternate sides by narrow glass tubes, which serve to convey the condensed vapours back to the distillation flask, whilst pools of condensed liquid are collected on pieces of platinum gauze placed at the base of each bulb. The composition and temperature of the liquid in these pools changes continually as the distillation proceeds, and thus their work is always proportioned to the composition of the mixture at each stage in the distillation. The Young and Thomas dephlegmator differs from the above in containing the communicating tubes of the successive divisions of the still-head inside, instead of outside, the main column; they are thus exposed to the temperature of the vapours from the distilled liquid instead of to that of the outside air, and to this change the efficiency of the apparatus is largely due. The divisions of the column are separated by pieces of platinum gauze, as in the Le Bel-Henniger dephlegmator.

Dephlegmators of this type are employed on the large scale for the purification of alcohol, aromatic hydrocarbons, and other liquids, with certain additions and refinements beyond the possibilities of laboratory practice.

A most valuable comparison of the efficiency of different forms of still-heads has been made by Young.<sup>1</sup> The figures in the following table summarise some of his results obtained in distilling a mixture of equal weights of benzene (B.P. 80°.2) and toluene (B.P. 110°.9). The distillate was collected in 11 fractions at intervals of about 3°, the residue after the boiling point of toluene had been reached forming a final twelfth fraction; the same rate of distillation (one drop of distillate per second) was maintained throughout, as it was found that this factor has a marked influence on the separation of the mixture, a much better separation being effected by diminishing the rate of distillation. The weight of vapour and liquid in the still-head

<sup>1</sup> *J. Chem. Soc.*, 1899, lxxv. 679.

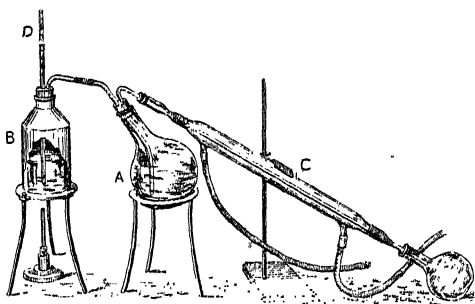
is the weight that was held back after the distillation was completed; 50 grams of the mixture were distilled in each case:—

Nature of Still-head.	Ordinary Distillation Bulb.	Hempel Still-head.	"Rod and Disc." 20 Discs.	"Pear" Still-head. 13 "Pears."	Le Bel-Henniger. 3 Bulbs.	Young and Thomas. 18 Sections.
Temperature Range.	Percentage Weight of Distillate.					
80.2 — 81.2	—	} 20.6	—	—	—	31.5
81.2 — 83.2	—		2.0	3.0	0.5	7.3
83.2 — 107.9	82.4	39.3	64.7	59.4	68.9	14.4
107.9 — 110.3	6.8	6.8	7.4	5.0	9.8	4.0
110.3 — 110.9	5.9	8.4	7.5	11.0	6.8	8.1
110.9 (Residue)	4.9	24.9	18.4	21.6	14.0	34.7
	100.0	100.0	100.0	100.0	100.0	100.0

Weight of vapour and liquid  
in still-head: grams - - 0.3 7.85 2.6 12.1

The inefficiency of the ordinary distillation flask is very apparent, more than 82 per cent. of the mixture being practically unchanged by the operation. The remarkable efficiency of the Young and Thomas dephlegmator is shown by the fact that over 70 per cent. of almost pure products, benzene and toluene, are separated. It is very noticeable in each case that the proportion of distillate within three degrees of the boiling point of toluene is markedly greater than that within the corresponding range from the boiling point of benzene; it appears to be a generality that the less volatile of the two constituents of a mixture is the more readily and completely separated. The above are the results of a single fractional distillation; in each instance one or more repetitions of the process are necessary in order to obtain pure products. The comparative number of fractionations required to effect this, with these different forms of apparatus, can be judged from these experiments.

*The Distillation of Non-miscible Liquids: Distillation by Steam.*—When a mixture of non-miscible liquids is distilled, the vapour pressure of the mixture, at any temperature, is approximately the sum of the vapour pressures of its constituents at that temperature. The liquids evaporate independently of each other, and their combined pressure will, therefore, overcome that of the surrounding atmosphere at a lower temperature than that of either of the constituents separately. This lower temperature is, of course, the boiling point of the mixture, since a liquid boils when its vapour pressure just exceeds the pressure of the surrounding atmosphere; the composition of the distillate remains constant at this temperature. These conditions form the basis of the very commonly adopted



process of *distillation by steam*. Very many substances of high boiling point, which are insoluble in water, are readily volatile with steam; the chief practical application of this volatility is as a means of separating substances from mixtures, or of removing organic compounds from the inorganic materials that have been made use of in their preparation. Hydrocarbons, such as naphthalene and anthracene, nitro-compounds and amines, such as nitrobenzene and aniline, and their homologues, are purified or isolated by this process, both in the laboratory and on the manufacturing scale. The apparatus shown in Fig. 11 illustrates the generally adopted laboratory method of steam distillation.



The substance to be distilled is placed in the flask A, together with sufficient water to fill the flask about one-third full; the flask is provided with a doubly-bored cork carrying two bent glass tubes, one of which communicates with the steam generator B, the other with the condenser C, as shown. The steam generator is provided with a pressure tube, D, and a receiver is placed at the end of the condenser. It is best to warm the contents of the flask A first, and then to attach the steam generator; the volatile substance separates from the water in the distillate as the distillation proceeds, and it is thus easy to ascertain when the distillation is complete.

Since a steam supply is usually at hand in any well-equipped laboratory, the generator can be dispensed with, the distillation flask (A), being attached directly to the steam supply. Super-heated steam is occasionally employed for the distillation of difficultly volatile substances. The temperatures at which some organic substances distil with steam, together with their boiling points, are given in the following table :—

SUBSTANCE.	DISTILS WITH STEAM AT :—	BOILING POINT.
Carbon tetrachloride	66.7°	76.6°
Benzene - -	69.1°	80°
Toluene - -	84°	110°
Nitrobenzene -	99°	209°
Naphthalene -	98.2°	218°

These distillation temperatures are for a pressure of 760 mm. By deducting the vapour pressure of water at the temperature of the distillation, from 760 mm. in each case, the vapour pressure exerted by the substance carried over by the steam is obtained. With benzene, for instance, the vapour pressure of water at 69°.1 is 224 mm.; the benzene, therefore, must account for the remaining pressure of 536 mm. In the case of nitrobenzene, since the vapour-pressure of water at 99° is 733 mm., only 1/28th of the total pressure, 27 mm., is due to the nitrobenzene. These relations have been checked by direct experiment in several cases. Despite this small contribution towards the total

vapour pressure in the case of substances of high molecular weight, the quantity converted into vapour and collected in the distillate is considerable. This quantity can be calculated from the vapour pressure of the substance at the temperature of distillation; the mixed vapour, and therefore the distillate, contains water and the substance distilled, in the ratio of the products of their molecular weights and vapour pressures at the temperature of the distillation. In the case of benzene (molecular weight 78), this will be  $\frac{78 \times 536}{760} = 55$  grams of benzene to  $\frac{18 \times 224}{760} = 5.3$  grams of water (molecular weight 18), or approximately 9.5 to 1. With nitrobenzene (molecular weight 123), the proportions are  $\frac{123 \times 27}{760} = 4.4$  grams nitrobenzene, and  $\frac{18 \times 733}{760} = 17.3$  grams water, or about 1 to 4. This relation shows that the relatively high vapour pressure of water is counterbalanced by its low molecular weight in respect to the composition of the distillate; the advantage of distilling substances of high molecular weight by means of steam is correspondingly evident.

## CHAPTER VII.

### THE SOURCES OF THE HYDROCARBONS.

The natural sources of the aliphatic hydrocarbons—Petroleum and its products; the refining and origin of petroleum.

Destructive distillation as a source of hydrocarbons—The destructive distillation of shale: the paraffin industry.

The destructive distillation of coal. Coal tar—Coal tar as a by-product from coke ovens—The working up of coal tar; coal tar products.

Synthetical applications of hydrocarbons—The mutual synthetical relations of aliphatic and cyclic hydrocarbons—The catalytic action of metals.

Terpenes, the hydrocarbons of essential oils.—Camphor.

FROM a theoretical standpoint the hydrocarbons form the basis for the study of organic compounds. But since the most readily accessible substances have naturally been made use of in carrying out synthetical investigations these "elements" of organic chemistry have quite as often been the goal, as they have been the starting-point of experimental work.

In the present chapter the sources of the hydrocarbons will be studied, their relations to each other and to other groups of compounds, their value in the synthesis of new substances and, in outline, their technical applications.

In the aliphatic group the saturated hydrocarbons, the paraffins, are typically inert. Since, moreover, they are not readily obtained in a condition of purity from their most prolific source, petroleum, their relation to other compounds has been chiefly studied by preparing them from the latter. In the aromatic group, on the other hand, pure hydrocarbons are readily accessible; also, they are, comparatively, very reactive and, therefore, serve as the starting-point in the practical investigation of many cyclic compounds. Unsaturated aliphatic hydrocarbons and saturated cyclic hydrocarbons (trimethylene, etc.) take

up an intermediate position, and offer a specially interesting path of study on account of their relation to derivatives of other hydrocarbons, both cyclic and aliphatic.

*The Natural Sources of the Aliphatic Hydrocarbons: Petroleum.*—Petroleum<sup>1</sup> or rock-oil (*oleum petrae*) is by far the most important natural source of hydrocarbons. It consists of a very complex mixture of these compounds, the nature of which varies considerably. The oil from the historic fields of Pennsylvania contains saturated aliphatic hydrocarbons almost exclusively, whilst the Russian petroleum of the Baku district consists chiefly of hydrocarbons called *naphthenes*, having the general formula  $C_nH_{2n}$ , and which are, most probably, saturated cyclic compounds of the hexamethylene type. In addition, some ten per cent. of aromatic hydrocarbons are present in the Baku oil, the aliphatic hydrocarbons and some complex oxidation products accounting for the remainder. Small quantities of aromatic hydrocarbons and of naphthenes are also present in American petroleum.<sup>2</sup>

American oil is still obtained by first drilling through the rocks to the requisite depth, and then either pumping out the oil or allowing it to flow; the oil frequently issues from the wells at great pressure, especially when first liberated. The discovery of flowing wells in 1861 gave a great impetus to the development of the Pennsylvanian oil fields. The yield per day rose from 200 barrels in 1860 to 15,000 barrels in 1862; it is now little short of 100,000 barrels. The raw product is conducted from the wells through pipe-lines to storage tanks, whence it is distributed to the refiners. In refining, the crude oil, after a suitable chemical treatment, is subjected to fractional distillation and thus separated into such commercial products as petroleum ether, naphtha, kerosene and lubricating oils, whilst vaseline is prepared from the residue that remains after distilling up to about 300°. These products are all mixtures of liquid hydrocarbons, from  $C_5H_{12}$  up to  $C_{18}H_{38}$ , except vaseline, which contains, in addition, some

<sup>1</sup> The most complete treatises on petroleum are—*Petroleum and its Products*, Boverton Redwood, 2nd edition, 1906; *The Production, Technology, and Uses of Petroleum and its Products*, Peckham, 1884; *Handbook on Petroleum*, Thompson and Redwood, 1901.

<sup>2</sup> Young, *J. Chem. Soc.*, 1898, lxxiii. 905

of the solid paraffins and some naphthenes. The low-boiling fractions are now used in large quantities in the combustion engines of motor vehicles (petrol, etc.). The portion which distils between  $150^{\circ}$  and  $200^{\circ}$  forms the ordinary paraffin oil as used for lighting and heating purposes. This oil should be free from low boiling constituents, since their vapours may easily form explosive mixtures with air and give rise to accidents. It is, therefore, of importance to determine the "flash point" of such burning oils. This is done by heating the oil gradually in a special apparatus and ascertaining the temperature at which the vapour ignites.

By means of further fractionation pure hydrocarbons can be isolated from the above mixtures. In this way the hydrocarbons of the paraffin series, from  $\text{CH}_4$  to  $\text{C}_{30}\text{H}_{62}$ , have been isolated from Pennsylvanian petroleum. Various hydrocarbons of the ethylene series have also been obtained, but it is possible that in many cases these are due to decompositions occurring during the distillation. This method of distillation is used for the preparation of pure pentane, which has been adopted as a standard of light in the form of the Harcourt pentane lamp.<sup>1</sup>

The petroleum of the Caucasus district is similarly worked up to commercial products, which although chemically very different from those obtained from Pennsylvanian oil, have analogous industrial applications; it differs chiefly in yielding less burning oil (kerosene), more lubricating oil, and a large, non-volatile residue which is extensively employed as fuel under the name of *astatki*.

Both at Baku and in America extensive exudations of gaseous hydrocarbons have been associated with the boring of petroleum wells, and in some cases have been given off at natural springs. The evolved gases consist of from 50 to 90 per cent. of methane, its homologues, ethane, propane and butane, together with small and varying proportions of olefines and carbon dioxide. The sacred fire at Baku<sup>2</sup> is supplied essentially by methane,

<sup>1</sup> Cf. Clowes, *Journal of Gas Lighting*, 1901, lxxvii. 1, 648.

<sup>2</sup> An account of the fire-worshippers of this district will be found in Dr. Hyde's *De Veteri Persorum, Medorum ac Parthorum religione historia*; London, 1760; p. 148. Also Jonas Hanway, *Historical Account of the British Trade over the Caspian Sea*; London, 1754; i. 263 and 381.

and, in the early days of the Pennsylvanian industry, gas from the Pittsburgh wells was conveyed to very considerable distances for lighting and heating purposes.

The origin of these naturally occurring hydrocarbons has been the subject of much discussion. Petroleum and the allied products, natural gas and bitumen, are very widely distributed; they occur in rocks of all ages, from the Silurian upwards, and their occurrence bears no relation to any one geological period. The oil-bearing rocks of North America are Primary limestones, sandstones, or conglomerates, those of the Caucasus, for the most part, Tertiary sandstones; they all possess a porous structure by virtue of which they act as a reservoir for the oil, and are covered by an impervious stratum of shale or marl. The proximity of mountain chains is also associated with petroleum deposits; the Alleghanies, for instance, in Pennsylvania, and the Caucasus in Baku. In the former district the most productive areas are in comparatively undisturbed strata, whilst in the latter the oil-bearing rocks have undergone considerable disturbance. From these differences in the conditions of occurrence it is highly probable that the oil has not always originated from the same source.<sup>1</sup> Its presence in limestone rocks is generally attributed to the decomposition of animal remains, though if this be the case, it is difficult to understand why such enormous quantities of petroleum should accumulate in one place. Such remains are characteristically absent from the sandstones of Pennsylvania and Baku, and it is, therefore, more probable that the oil is not indigenous to the rocks in these districts, but has resulted from a destructive distillation of the overlying shales. The conditions under which the decomposition of organic matter, either vegetable or animal, has occurred, can hardly be reproduced in the laboratory, because the high temperature and pressure in the interior of the earth must have played an important part in regulating the nature of the changes, which it is difficult to imitate. Animal matter, for instance, yields a

<sup>1</sup> Literature on the Origin of Petroleum:—*Report on the occurrence of Petroleum, Natural Gas, and Asphalt Rock in Western Kentucky*, 1891; by Dr. Orton. Sierry Hunt, *Chem. News*, 1862; v. 5, 16, & 35. Anderson, *British Association Reports*, 1889; p. 725.

product very different from petroleum under the ordinary conditions of destructive distillation, a product containing many basic substances. But Engler has shown that fats yield a true petroleum oil when distilled under a pressure of ten atmospheres and at a temperature of from  $300^{\circ}$  to  $400^{\circ}$ , and he has succeeded in isolating hydrocarbons from pentane up to nonane from the distillate thus obtained.<sup>1</sup> This indicates the possibility of an animal origin, although Engler failed to obtain a similar product by the decomposition of animal remains, and was, therefore, forced to the conclusion that a preliminary change must have occurred, previous to the formation of the petroleum, whereby all nitrogenous and other substances were removed except fat. The vegetable origin of petroleum is more in accord with known data, since it is the normal distillation product of shale, though here again the pressure and temperature in the earth would make the conditions of decomposition different from those of ordinary destructive distillation; in addition, water is likely to have been an important factor, for common salt, either in solution or in the solid state, is almost invariably associated with petroleum. Coal, as well as shale, may have given rise to oil under these conditions, but such a vegetable origin is of necessity restricted to deposits in rocks containing, or in close proximity to, such organic material.

The paucity of organic remains in many oil-bearing strata, especially in the Baku district, has suggested an inorganic origin of petroleum to many observers. Mendeléeff<sup>2</sup> regarded its formation as due to the action of water which had penetrated through fissures in the earth's crust, such as are formed during periods of geological change or by volcanic action, on carbide of iron. That hydrocarbons result from such an action is well known, and the more recent investigations of Moissan on other carbides show that a variety of hydrocarbons are formed in their decomposition.<sup>3</sup> Further, it has been shown experimentally that when the hydrocarbons resulting from these carbides are exposed to a high temperature,

<sup>1</sup> *Berichte*: 1888, xxi. 1,816; 1889, xxii. 592; and 1900, xxxiii. 7. *angew. Chem.*, 1908, xxi. 1,585.

<sup>2</sup> Cf. Anderson, *British Association Reports*, 1889; p. 725.

<sup>3</sup> Chap. iv., pp. 51 and 52.

especially in presence of hydrogen, aided by the catalytic action of finely divided metals (*cf.* p. 116) they give products which closely resemble petroleum, and that by modifying the conditions, products similar to Caucasian, Galician, and American petroleum may be prepared artificially. It is highly probable that carbides are present in the interior of the earth, and that water has had access to the oil-bearing strata has already been mentioned; but the stratigraphical distribution of petroleum, and the fact that it so often occurs in undisturbed strata, are strong arguments against this view of the general origin of petroleum, although its formation in certain isolated districts may have been due to such a decomposition. The optical activity of petroleum (*cf.* Chap. xii., p. 316) has been adduced as evidence that the hydrocarbons of which it is composed have resulted from the decomposition of animal or vegetable remains, principally the latter, which were in themselves optically active.<sup>1</sup>

A remarkable natural occurrence of a paraffin is that of normal heptane,  $C_7H_{16}$ , in the resin sap of the Californian digger pine (*Pinus sabiniana*). This sap yields a liquid distillate consisting almost entirely of normal heptane.<sup>2</sup> Solid paraffins constitute another natural product called *Ozokerite*, or mineral wax, which is worked in Galicia for the preparation of pure paraffin; the refined product is often known as *Ceresine*.

*Destructive Distillation as a Source of Hydrocarbons. The Destructive Distillation of Shale; the Paraffin Industry.*—Destructive distillation is the term applied to the decomposition by heat of organic products such as wood and coal, in absence of air. Were a full access of air permitted to such products, ordinary combustion would, of course, ensue upon heating, with the formation of carbon dioxide and water from the contained carbon and hydrogen respectively. In absence of air, the process is in part destructive, in part constructive, with the result that products of four different kinds are obtained by the decomposition—namely, permanent gases, an aqueous distillate, an oil or tar insoluble in water, and a

<sup>1</sup> Walden, *Chem. Zeit.*, 1906, xxx. 391, 1, 155, 1, 167. Engler, *Ibid.*, 1906, xxx. 711.

<sup>2</sup> T. E. Thorpe, *J. Chem. Soc.*, 1879, xxxv. 296.



carbonaceous residue such as charcoal or coke. The composition of these products varies very greatly according to the nature of the substance distilled and the temperature at which the decomposition is effected, especially in the case of the liquid distillates.

As shown in the following table, carbon is the chief constituent of what may be termed the "ores" of organic chemistry; next in order of quantity is oxygen, and then hydrogen, the remainder of the constituents being present only in very small proportions. The gradual passage from wood to anthracite is accompanied by a loss in oxygen and hydrogen, with a corresponding increase in the percentage of carbon; and whilst the conditions of formation of peat, lignite, bituminous coal, cannel coal, and anthracite are not to be regarded as successive changes of a strictly analogous character, still, from the standpoint of their ultimate composition, there is a gradual and similar change in passing from the younger to the older fossils:—

*Average Percentage Composition of Wood, Peat, Lignite, and Coal.*

	Carbon.	Hydrogen.	Oxygen.	Nitrogen.	Sulphur.	Ash.
Wood (Oak) .	49.7	6.0	41.3	1.3	—	1.7
Peat . . .	58.3	6.4	31.3	1.3	—	2.7
Lignite . .	66.3	5.6	22.9	0.6	2.4	2.2
Bituminous Coal	77.8	5.2	9.0	1.3	1.0	5.7
Cannel Coal .	79.2	6.1	7.3	1.2	1.4	4.8
Anthracite .	90.1	4.3	2.0	1.0	0.9	1.7

Of the two factors that influence the composition of the oil or tar obtained by destructive distillation, wood and the younger fossils yield, essentially, aliphatic compounds, true coal, aromatic compounds; a low temperature favours the formation of the former, a high temperature that of the latter. Further, oxygenated compounds are more readily formed at low temperatures, and with a product such as wood, which is generally distilled at about 500°, and which itself contains a considerable proportion of oxygen, they form almost the entire liquid distillate in the form of methyl alcohol (wood spirit) and acetic acid; the evolved

gas also contains oxygenated compounds (carbon monoxide and carbon dioxide) in addition to hydrogen and hydrocarbons. The results obtained by Young (1850) in the distillation of Boghead Cannel, one of the younger fossils, led to the founding of the Scotch paraffin industry; since the exhaustion of the original cannel, bituminous shales have been employed, whilst brown-coal is the raw material for the paraffin industry in Germany. These shales and coals are distilled at a full red heat in presence of steam; the distillate, after the separation of the ammoniacal liquor, is washed with alkali and acid successively to remove acid and basic constituents, and is then fractionated, when first burning and lubricating oils pass over, and finally solid paraffin. The last forms about 12 per cent. of the crude oil, and consists of the solid hydrocarbons of the paraffin series; its chief use is for the manufacture of paraffin candles and night-lights.

*The Destructive Distillation of Coal; Coal Tar.*<sup>1</sup>—The distillation of coal at a high temperature, as employed in the manufacture of illuminating gas, is the chief source of the aromatic hydrocarbons. The relative value of the products of distillation—coke, tar, ammoniacal liquor, and illuminating gas—has undergone many changes since the early days of the coal gas industry some eighty years ago. At that time the manufacture of illuminating gas was the sole object of the distillation; the tar and ammoniacal liquor were regarded as necessary evils of the process, as by-products of no value. To-day a very different relation obtains; both from a scientific and economic standpoint the value of the tar and liquor is an all-important factor in governing the conditions of distillation. No more fascinating story has been revealed, either in pure or applied science, than that of the coal tar industry, which began with Hofmann's discovery of benzene in the more volatile portions of coal tar in 1845, and Perkin's preparation of the first aniline colour, "Perkin's mauve," in 1856. Runge had previously discovered phenol and aniline in coal tar (1832), and had prepared an artificial dye called rosolic acid.

<sup>1</sup> Literature on Coal Tar:—G. Lunge, *Coal Tar and Ammonia*, 1887; 2nd edition, 1901. R. Meldola, *Coal, and What we get from It*, 1891 (a simple account of the coal tar industry).

Coal tar is a mixture of a most complex character, in which the presence of some 140 different substances has been established. One by one, the most prominent of these have become, on the one hand, the starting-point for important industrial products, and, on the other, they have provided the material for unravelling the structure and relations of the aromatic compounds. Faraday had in 1825 discovered the presence of benzene in illuminating gas, but apart from this a few naturally-occurring products, such as the benzaldehyde of oil of bitter almonds, the benzoic acid of gum benzoin, and the hippuric acid found in the urine of herbivora, were the only sources of aromatic compounds accessible to the investigator. Liebig and Wöhler, in their classical investigation on the "Radical of benzoic acid,"<sup>1</sup> first elucidated the complexities of the group; but further work was slow, owing to the inaccessibility of material for study. This material has now been supplied in abundance by the constituents of coal tar.

Under the ordinary conditions of distillation adopted in the manufacture of coal gas, using fireclay retorts and a temperature of 1000° to 1100°, one ton of Lancashire coal yields on an average 10,000 cubic feet of gas, 12 gallons of tar, 30 pounds of ammonium sulphate, and 13 cwt., or 65 per cent., of coke. The chief constituents of the tar are aromatic hydrocarbons (benzene and its homologues), naphthalene, and anthracene, together with oxygenated derivatives, of which phenol and its homologue cresol are the most important; a small proportion of basic constituents, aniline, pyridine, and quinoline are also present. Aliphatic hydrocarbons are typically absent in the tar, but the gas contains some 35 per cent. of marsh gas, a little ethane, and about 6 per cent. of unsaturated hydrocarbons, chiefly ethylene. In addition, benzene and naphthalene remain suspended in the gas, and contribute considerably to its illuminating value; they are carried along by the gas in the form of a fine mist. In 1883, when the price of benzene was high, many processes were tried for depriving the gas of these hydrocarbons; the gas suffered in consequence, and more normal economic relations amongst the products of distillation soon accentuated the futility of the

<sup>1</sup> Cf. Chap. ii. p. 15.

method. From another source, however, the coke industry, similarly suspended hydrocarbons have become an important raw material.

*Coal Tar as a By-product from Coke Ovens.*—For the preparation of the coke used for metallurgical work, coal was, until some 40 years ago, carbonised in the so-called “beehive” ovens, in which the decomposition is effected with partial access of air and at a comparatively low temperature. The products are of the same nature as in the manufacture of coal gas, but the coke was the sole object of the industry, and the gas, tar, and ammonia were allowed to escape free; in 1880 the loss of the ammonia alone in this country was valued by the late Dr. Angus Smith at no less a sum than £2,800,000. Attention has naturally been turned to the recovery of these by-products, but the tar obtained from this source proved far less valuable than was expected. Like all low temperature products it is rich in paraffin hydrocarbons and higher oxygenated compounds, such as creosol and guaiacol, whilst it is very poor in benzene, anthracene, and phenol. The more recent forms of coke oven are closed, the coal being carbonised without access of air, and at a temperature somewhat higher than that adopted in the manufacture of coal gas; the result of this change in the method of preparing coke has been to yield a tar which is practically the equivalent of the product from gas works. The gas given off in the distillation is at present generally used for heating purposes only, thus allowing of the removal of the hydrocarbon vapours referred to above, and this source of benzene and its homologue, toluene, has become one of great economic importance. There is more than twenty times as much of these hydrocarbons in the gas as there is in the tar that is simultaneously produced.

*The Working-up of Coal Tar; Coal Tar Products.*—These two industries, in which coal is destructively distilled, supply the raw material for the manufacture and investigation of aromatic compounds. To isolate the chief constituents of coal tar, the crude product, a dark, thick liquid containing a considerable proportion of finely divided carbon, is subjected to a series of distillations and chemical washings. In the first distillation *light oils* (up to  $170^{\circ}$ ), *carbolic oil* ( $170^{\circ}$ - $230^{\circ}$ ), *creosote oil* ( $230^{\circ}$ - $270^{\circ}$ ), and *anthracene*

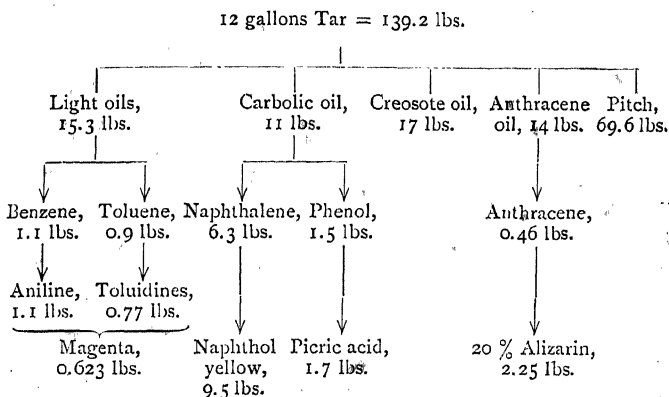
oil (above  $270^{\circ}$ ) are obtained successively; the residue is used for the manufacture of pitch. Each distillate is then worked up according to requirements. The light oils consist essentially of the benzene hydrocarbons; these are washed with alkali and acid to remove acid and basic constituents respectively, and then fractionated. This fractionation is conducted with very efficient apparatus constructed on the principles explained in Chapter VI., and chemically pure benzene and toluene are thus obtained. The preparation of products of this remarkable degree of purity has been found more advantageous than the subsequent purification of the derived compounds, such as the coal tar colours, or the intermediate products from which they are prepared.

Carbolic oil, the next fraction in the distillation, is worked up to naphthalene, an important hydrocarbon for the manufacture of colours, and to carbolic acid (phenol), which is used for the preparation of explosives and colours, as well as for antiseptic and disinfecting purposes. Creosote oil is employed in the crude state for pickling timber and for illuminating and heating purposes. The final distillate, the anthracene oil, is a mixture of a large number of complex cyclic hydrocarbons, from which the anthracene is separated by washing with suitable reagents; this product is not worked up to the degree of purity adopted in the case of benzene, as it has been found more economical to start the manufacture of alizarin from 60 or 80 per cent. anthracene. Whilst these products represent the chief coal tar constituents from the manufacturer's standpoint, it is to be borne in mind that the associated compounds, which occur in smaller quantities, have been the raw material for numerous scientific investigations. Thiophene, a sulphur analogue of benzene, was the unknown companion of coal tar benzene till discovered therein by Victor Meyer (1883), a discovery which opened a whole chapter of new compounds; nor is the field by any means exhausted. Coal tar, the once despised by-product, has proved itself "the army of aromatic compounds, . . . an indispensable helpmate of the chemical investigator, the physiologist, the bacteriologist, the medical practitioner, and serviceable to the many-sided requirements of the art of colour-making, painting, colour-

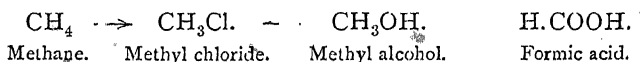
printing, and of the manufacture of explosives.”<sup>1</sup> Hence, an inseparable connection has arisen between the coal tar industry and the pure science of the aromatic compounds.

In the appended table the quantitative relations of the chief coal tar products and some simple derivatives, as obtained from the destructive distillation of coal, are tabulated.

One ton of Lancashire coal yields:—

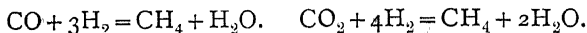


*Synthetical Applications of Hydrocarbons.*—The characteristic inactivity of the hydrocarbons of the marsh gas or paraffin group renders them of little value as the starting-point for synthetical preparations. Chlorine and bromine are the only reagents that attack them easily; these form halogen substitution products, such as ethyl chloride and ethyl bromide,  $C_2H_5Cl$  and  $C_2H_5Br$ , but even these derivatives are more accessible from the alcohols of the series. By means of reducing agents the halogen derivative can be reconverted into the hydrocarbon, a process which is termed “inverse substitution.” Such a series of changes as the following:—



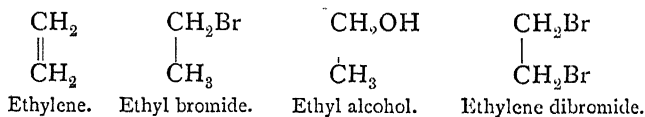
<sup>1</sup> H. Caro, Address to the German Chemical Society: “Ueber die Entwicklung der Theerfarben-Industrie,” *Berichte*, 1892, xxv. 955.

can, indeed, be effected from the hydrocarbon, but the reverse process has been more commonly adopted, and the structure of an alcohol or acid determined by ascertaining the nature of its mother-substance, the corresponding hydrocarbon. There is a special interest, however, in the fact that methyl alcohol can be prepared from methane, because the latter can be obtained directly from the elements carbon and hydrogen.<sup>1</sup> Also, carbon combines directly with oxygen to form carbon monoxide and carbon dioxide, and when either of these gases is mixed with hydrogen, and passed over finely divided nickel at a temperature of from 250° to 300° it is completely converted into methane and water.<sup>2</sup> These changes are represented by the equations:—



This forms a complete synthesis of the hydrocarbon. Since methane can be converted into methyl alcohol, this into ethyl alcohol, acetic acid, and other more complex compounds, the complete synthesis of these compounds from their elements can be thus achieved. Such syntheses are typical of the progress that has been made since the time when Berzelius and Gmelin regarded organic compounds as incapable of being produced in the laboratory.

Unsaturated hydrocarbons, such as ethylene and acetylene, are of greater synthetical value, since they are much more reactive; thus, under the influence of several reagents they are readily converted into such saturated compounds as ethyl bromide, ethyl alcohol, and ethylene dibromide:—



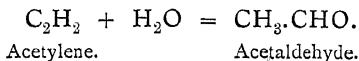
From the last (ethylene dibromide), succinic and tartaric acids can be obtained, and thus, with a simple hydrocarbon as the starting-point, a region of fairly complex substances

<sup>1</sup> Cf. Chapter iv. 54.

<sup>2</sup> Sabatier and Senderens, *Comptes rend.*, 1902, cxxxiv. 514.

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is approached. Acetylene, which can be prepared directly from the elements, readily takes up water when it is passed into sulphuric acid and the diluted solution is boiled, to form acetaldehyde:—



and from this numerous important syntheses are possible. With the exception of acetylene, however, these unsaturated hydrocarbons are not directly accessible; they are best prepared from alcohols or acids, and, therefore, their synthetical value is essentially indirect.

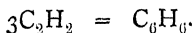
The aromatic hydrocarbons stand in marked contrast to the above. Not only are they by far the most accessible compounds of the group, and readily obtained in a state of purity, but they are acted upon by reagents such as nitric and sulphuric acids, halogens, and oxidising agents, with the formation of compounds from which practically all other derivatives of the group can be prepared. These direct reactions are easily carried out and controlled, and so thoroughly have they been studied that the conditions governing the formation of one or other of the many isomeric substitution products that can arise, are accurately known. This latter factor has been of the greatest value in the study of the group; it will be dealt with in some detail in Chapters VIII. and X. Despite this reactivity, it is to be remembered that the nucleus of six carbon and six hydrogen atoms in benzene itself is extremely stable, and, therefore, that the synthetical value of the aromatic hydrocarbons is chiefly restricted to cyclic compounds.

*The Mutual Synthetical Relations of Aliphatic and Cyclic Hydrocarbons.*—The characteristics of benzene and its derivatives are so entirely different from those of aliphatic compounds, that it is not surprising to read the statement in Kekulé's *Lehrbuch* (1866) that "no instances of the passage of aromatic substances into compounds of the fatty group, or of the reverse change of fatty compounds into aromatic substances, or at least any that can be effected by comparatively simple reactions, are as yet known with certainty." To-day, however, a considerable number of such changes are known, some of which can be effected by simple and direct reactions, and the marked

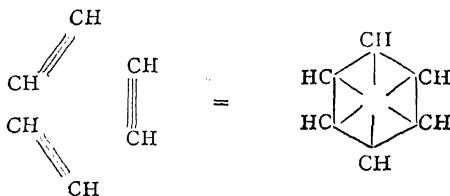


contrast in the properties of the compounds concerned has invested these changes with a special interest.

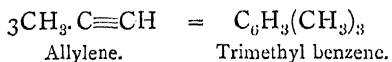
The polymerisation of acetylene and its homologues, which can be effected by simply heating, leads to the formation of cyclic hydrocarbons. Acetylene itself forms benzene, methyl-acetylene (allylene) forms trimethylbenzene, and halogen derivatives of acetylene form halogen substitution products of benzene. The first change is represented by the simple equation:—



or graphically:—



and similarly:—



The preparation of ethane from ethylene and of the latter from acetylene represent the methods by which aliphatic hydrocarbons can be prepared from less saturated compounds. This direct addition of hydrogen can be effected by passing the vapour of the hydrocarbon, mixed with hydrogen, over finely divided nickel; aromatic hydrocarbons and their derivatives are similarly reduced to their saturated hydrides, benzene to hexahydrobenzene (hexamethylene), aniline to aminohexamethylene (cyclohexylamine), and phenol to hydroxy-hexamethylene (cyclo-hexylalcohol).<sup>1</sup> The preparation of methane by the reduction of oxides of carbon with hydrogen, in presence of nickel, has been referred to before (p. 114);

<sup>1</sup> Sabatier and Senderens, *Comptes rend.*, 1900 to 1904, vols. cxxx. to cxxxviii. The results are fully summarised in *Comptes rend.*, 1905, cxli. 44.

it is from this effect of nickel and other metals (platinum, cobalt, copper, iron) when in a state of fine division that Sabatier and Senderens deduced their hypothesis of the origin of petroleum from metallic carbides (p. 107).

This direct addition of hydrogen proceeds to only a very limited extent in absence of the nickel, and then only at a high temperature; in presence of the metal the reduction can, in most cases, be effected between 150° and 250°, but still the nickel itself does not appear to undergo any change. There are very many reactions of this character in which the progress of a chemical change is greatly accelerated by the presence of a third, apparently indifferent substance. The term *catalysis*, originally introduced by Berzelius, is generally used for reactions of this class, and the agent which effects the catalytic action is spoken of as the *catalyst*, *catalyser*, or *catalytic agent*. The chief characteristic of a catalyst<sup>1</sup> is that it changes the velocity of a reaction without being itself altered by the process; its action has been aptly compared to the influence of the whip on a horse, or of oil on the wheels of a machine (Ostwald). Most catalysts act like nickel as accelerators of chemical change, but some are known which reduce the velocity of a reaction; these have been called "negative catalysts."<sup>2</sup> It is probable, however, that such negative catalysts act merely by destroying positive catalysts.<sup>3</sup> In addition to the metals already mentioned, many others exert a catalytic action, and several other classes of substances, such as metallic oxides and salts, charcoal, pumice, glass, mineral acids, and enzymes, are included among the well-known catalysts.

The very interesting fact has been observed that the influence of finely divided platinum and other metals is, in many respects, analogous to that of enzymes. Thus, Schade<sup>3</sup> has shown that the fermentation of sugar to form alcohol and carbon dioxide can probably be effected by finely divided metals, and has pointed out many analogies between such catalytic processes and ordinary fermentation. The hydrolysis of glucosides has been similarly effected with the

<sup>1</sup> Cf. Bigelow, *Z. physik Chem.*, 1898, xxvii. 585.

<sup>2</sup> Titoff, *Z. physik Chem.*, 1903, xlv. 641.

<sup>3</sup> *Z. physik Chem.*, 1906, lvii. 1.

help of platinum black.<sup>1</sup> A remarkable feature of such processes is that certain substances, such as hydrocyanic acid, act as poisons towards the catalyst and inhibit its action. The mode of action of catalysts is not at present understood; several hypotheses have been put forward, but no generally acceptable explanation of their work has as yet been suggested.<sup>2</sup>

Apart from this direct reduction and such methods as that already given for the preparation of trimethylene,<sup>3</sup> the most important of the reactions in which cyclic compounds result from open-chain substances are concerned with somewhat complex derivatives of the hydrocarbons, especially acids and esters.<sup>4</sup> Of the reverse change, from aromatic to aliphatic compounds, the known instances are far less numerous. In some cases the benzene ring is simply broken by the reagents employed, and the resulting product contains the six carbon atoms intact as an aliphatic compound; in others, one or more atoms of carbon are eliminated in the decomposition, and some reactions of special interest are known in which one carbon atom of the ring is removed and a five-membered cyclic compound formed.

The conversion of the aliphatic into cyclic hydrocarbons, other than by comparatively simple and direct reactions such as the above, can hardly be regarded as synthetical from a modern standpoint, though it claims some historic and technical interest. Thus, by passing the vapour of various hydrocarbons through red-hot tubes, or over heated surfaces of any kind, extremely complex changes occur, conditioned by temperature, the rate at which the decomposition is allowed to proceed, and the nature of the hydrocarbons employed. Such pyrogenetic reactions, which were first studied by Berthelot,<sup>5</sup> are, like destructive distillation, partly destructive and partly constructive. Methane is thus decomposed to a certain extent into its constituent elements, carbon and hydrogen, but more complex hydro-

<sup>1</sup> Neilson, *Amer. J. Physiol.*, 1905, xv. 148.

<sup>2</sup> Cf. *Chemical Statics and Dynamics*, J. W. Mellor, 1904, chapter x.; also "Die Lehre von der Reaktionsbeschleunigung durch Fremdstoffe (Katalyse)," W. Herz, *Sammlung chem. u. chem-technischer Vorträge*, 1906.

<sup>3</sup> Chapter V., p. 62.

<sup>4</sup> Cf. Chapter IX., pp. 177 to 179.

<sup>5</sup> *Chimie organique fondée sur la Synthèse*, Berthelot, 1860; and *Les Carbures d'Hydrogène*, Berthelot, 1902.

## SOURCES OF THE HYDROCARBONS.

carbons such as benzene and naphthalene are formed, together with ethylene and acetylene; ethylene forms both aromatic and aliphatic hydrocarbons, acetylene, at a dull red heat, benzene, but at a higher temperature it is almost completely decomposed into its elements and methane. Benzene and other cyclic hydrocarbons form more complex cyclic substances, such as naphthalene and anthracene, but at the same time acetylene and simple paraffin hydrocarbons result. The effect of increasing temperature with all organic compounds is towards complete decomposition into carbon and hydrogen, and, short of this, the formation of compounds relatively rich in carbon and poor in hydrogen. Hence, at the high temperature of a gas retort or coke oven the more highly hydrogenised aliphatic hydrocarbons are decomposed into hydrogen and compounds of higher carbon density such as benzene, naphthalene, and anthracene. This is the final result, but many intermediate stages undoubtedly occur; the formation of benzene and naphthalene from methane, ethane, or ethylene may proceed directly or *via* acetylene to benzene, the latter with an additional supply of acetylene forming naphthalene. Such considerations serve to explain the extraordinary variety of products found in coal tar.

The technical interest of pyrogenetic reactions has arisen from attempts to convert petroleum, or more especially the residue from its distillation (*astatki*), into the more valuable products benzene and anthracene, by the action of heat. The experiments have met with but limited success, and the present excessive supply of coal tar has not encouraged investigation in this direction.

*Terpenes, the Hydrocarbons of Essential Oils.*<sup>1</sup>—A group of naturally occurring hydrocarbons remains to be mentioned—the *Terpenes*. They form the chief constituents of the essential oils, the value of which in perfumery and in the manufacture of essences has long been recognised. The fruit and flowers of most plants owe their characteristic odour to the presence of these essential oils, which differ

<sup>1</sup> Literature on the Terpenes and Essential Oils:—F. Heusler, *Chemistry of the Terpenes*, trans. by F. J. Pond, 1902; E. J. Parry, *The Chemistry of Essential Oils and Artificial Perfumes*, 1899; E. Gildermeister and F. Hoffman, *The Volatile Oils*, translated by E. Kremers, 1900.

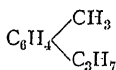
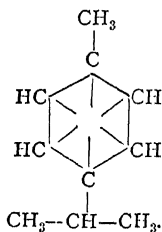
from the fatty vegetable oils, such as palm oil and linseed oil, in being readily volatile, especially with steam. Turpentine, the best known of these compounds, is prepared by distilling pine-tree sap with steam, when the essential oil passes over, leaving a non-volatile resin behind, known as colophony. The chief constituent of the oil is a hydrocarbon called *pinene*; it is present in many other essential oils, such as those of laurel, thyme, and lemon, and has the molecular formula  $C_{10}H_{16}$ . Isomeric hydrocarbons form the characteristic constituents of many other essential oils. These hydrocarbons, which are grouped together under the generic name of *Terpenes*, are characterised by the ease with which they pass from one into the other under the influence of heat or of simple reagents such as hydrochloric acid; also, they are readily transformed into aromatic compounds, and upon oxidation yield well-defined acids. These latter changes have served as the basis for the study of their structure, a problem which, though formerly regarded as comparatively simple, has since been shown to be beset with considerable difficulties. A very large amount of experimental inquiry has been devoted to this group, one member of which, called *dipentene*, has been synthetically prepared by W. H. Perkin,<sup>1</sup> whilst the structure of several of the simpler terpenes has been now almost completely elucidated. A few simple considerations will indicate the essential difficulty of the problem.

Pinene behaves as an unsaturated compound of the ethylene type, and like all terpenes, combines readily with bromine and with hydrochloric acid; the resulting compounds are crystalline substances, and owing to the ease with which they can be purified, they have been very helpful in the experimental study of the group. This behaviour points to the presence of an ethylene bond in the molecule. The dibromide of pinene is converted into an aromatic hydrocarbon, cymene (methyl-isopropyl benzene) when heated, and pinene itself yields the same compound when treated with iodine. Cymene has the formula  $C_{10}H_{14}$ , and differs, therefore, from pinene by containing two hydrogen atoms less than the latter. The structure of cymene is known with certainty, but there

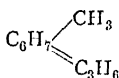
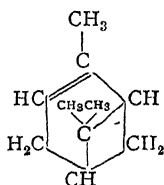
<sup>1</sup> *J. Chem. Soc.*, 1904, lxxxv. 654.

are several ways in which it might add two atoms of hydrogen to form a compound  $C_{10}H_{16}$  containing one ethylene bond. Following the relation of benzene to its reduction products, cymene could add two hydrogen atoms to form a dihydrocymene  $C_{10}H_{16}$ , but the resulting product should behave as a compound containing two double bonds. Some terpenes do add the four atoms of hydrogen required by such a compound, but pinene does not; it only takes up the two atoms. To account for this the second double bond must be eliminated, but without causing any change in the composition of the molecule, and it is the nature of this difference in structure that has been difficult to decide.

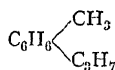
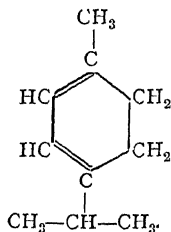
The study of the oxidation products of the hydrocarbon has, within recent years, sufficed to solve this difficulty, and the structural formula for pinene can now be regarded as satisfactorily established. It consists of a reduced benzene ring, having two carbon atoms in the meta-position linked across the ring by an intermediate carbon atom, to which two methyl groups are attached. This method of linking has been termed a *bridged-ring*; it is a special characteristic of the terpenes and related compounds. The relation of pinene to cymene and its difference from a dihydrocymene is shown in the following formulæ; its conversion into the former involves, it will be seen, the destruction of the "bridge" of the pinene-molecule:—



Cymene.  
(Para-methylisopropylbenzene).

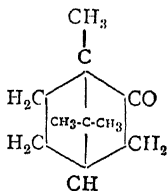


Pinene,



Dihydrocymene,

The terpenes have an additional interest on account of their simple relation to other constituents of the essential oils, which contain oxygen. Of these, *camphor* and *Borneo camphor*, or *borneol*, are the most important. Camphor has the formula  $C_{10}H_{16}O$ , and differs, therefore, from the terpenes only by the presence of an atom of oxygen; this can be added by direct oxidation to one of the terpenes (camphene), and the close relation of camphor to the terpenes is further shown by its conversion into cymene or cymene derivatives by comparatively simple reactions. But the simplicity of these relations ends here. The chemistry of camphor has proved most complex, and it is only after much difficult and detailed investigation that a satisfactory structural formula has been established.<sup>1</sup> Of the many formulæ that have been suggested, the following, proposed by Brecht, fulfils the requirements indicated by the chemical behaviour and relations of camphor and its derivatives. It has been deduced especially from the study of the oxidation products of camphor, several of which have been prepared synthetically, and it has now been conclusively established by the synthesis of one of these oxidation products, camphoric acid,<sup>2</sup> which can be converted into camphor:—



Brecht's formula for Camphor.

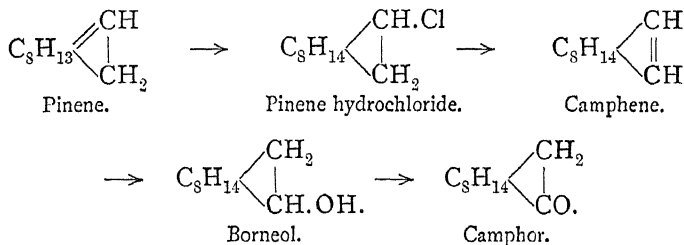
The relation of camphor to pinene is apparent in this formula; it also contains a bridged-ring, the orientation of which, however, is different from that of pinene.

During the past few years many attempts have been made to prepare camphor synthetically from the pinene of oil of turpentine, some of which are said to give a fair yield of camphor, and promise to become of industrial

<sup>1</sup> Cf. A. Lapworth, *British Association Reports*, 1900, p. 299.

<sup>2</sup> G. Komppa, *Berichte*, 1903, xxxvi. 4332.

value.<sup>1</sup> The stages in the chief methods employed in this synthesis consist in the successive conversion of pinene into its hydrochloride, of the hydrochloride into camphene, which is then converted into borneol, the alcohol of camphor, which is finally oxidised to camphor. The following formulæ illustrate this method:—



Apart from the study of the structural formulæ of these compounds, important advances have been made during the last few years in the synthetical preparation of the perfumes of flowers. Vanillin, the essence to which the sweet smell of the vanilla pod is due, and coumarin, the active principle of the Tonka bean, are now manufactured by synthetical methods, whilst a probable isomer of the odoriferous principle of violet, which also possesses its characteristic perfume, has been prepared by Tiemann & Krüger,<sup>2</sup> and is now a commercial product called *Ionone*. Many substitutes for natural perfumes are also known, such as artificial musk (trinitro-butyltoluene), heliotropin or piperonal, which possesses the odour of heliotrope, and anisic aldehyde, which has the perfume of hawthorn.

The technical applications of the essential oils have also been developed by the isolation of the active principles of certain oils from the mixtures in which they occur naturally, thus effecting greater reliability in their character and economy in their use.

<sup>1</sup> Cf. F. T. Pond, *J. Soc. Chem. Ind.*, 1907, xxvi. 383.

<sup>2</sup> *Berichte*, 1893, xxvi. 2675; 1895, xxviii. 1,754; 1898, xxxi. 808, 867.



## CHAPTER VIII.

### DERIVATIVES OF THE HYDROCARBONS.

The halogen substitution products of the hydrocarbons.

Derivatives of the hydrocarbons containing oxygen: Alcohols, Ethers, Acids, Aldehydes, and Ketones. Autoxidation.

Some typical derivatives of alcohols, acids, and phenols.

Derivatives of unsaturated hydrocarbons.

Derivatives of the hydrocarbons containing dissimilar substituents.

The influence of the molecular position of substituents on the properties of compounds: "Steric hindrance."

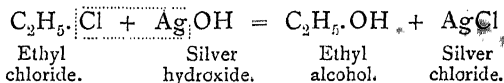
THE derivatives of the hydrocarbons form the chief subject-matter of organic chemistry. It is not the purpose of this book to deal with them in detail, either in respect to their methods of preparation, physical properties, or characteristic reactions; such data will be found in the ordinary text-books on organic chemistry. The object of this and the two following chapters is rather to show, by means of the chemical behaviour of some of the most important groups of compounds, the methods and lines of inquiry that have been adopted in the study of their structure and mutual relations.

By the replacement of one or more hydrogen atoms in a hydrocarbon by a substituting element or radical, the new molecule acquires certain chemical and physical properties depending upon the nature of the substituent. Whilst these properties are similar in kind amongst all groups of hydrocarbons, the nature of the latter and the position of the substituent in the molecule have each a specific influence on the behaviour and stability of the resulting compound. Such differences are especially apparent between aliphatic and cyclic substances. The characteristics of any one substituent are repeated when a second, like substituent is introduced, and the larger the number of hydrogen atoms in a hydrocarbon that are thus replaced

the more accentuated does the influence of the substituent become. When the hydrogen atoms are replaced by several dissimilar groups or atoms, then the properties of the new compound are a resultant effect depending on the nature and chemical character of each of the substituents.

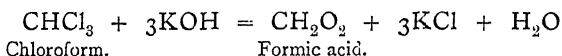
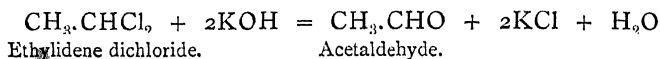
Associated with each group of substitution products are general methods of preparation and typical reactions; the former are made use of in the synthetical preparation of new compounds, the latter in investigating natural or laboratory products of unknown constitution. These generalities have already been spoken of;<sup>1</sup> they are the basis of the experimental methods of investigation, but owing to the variations they undergo on account of the influence of collateral substituents and of differences in structure of the parent substances, they form by no means such an easy path for inquiry as might be gathered from their stereotyped fixity in elementary text-books.

*The Halogen Substitution Products of the Hydrocarbons.*—These serve as a simple illustration of the above considerations. They are obtained both from aliphatic and aromatic hydrocarbons by the direct action of chlorine or bromine, and indirectly iodine and fluorine can be substituted for hydrogen. Such compounds as ethyl iodide,  $C_2H_5I$ , and brombenzene,  $C_6H_5Br$ , are liquids, insoluble in water, which can be reduced to the corresponding hydrocarbons. Brombenzene, however, requires a more powerful reducing agent for this change than is the case with ethyl iodide, and this greater stability of the aromatic haloid compounds is shown in their behaviour towards all reagents. These compounds may be regarded as derivatives of the halogen acids in which the hydrogen is replaced by an organic radical. The aliphatic halogen compounds are converted into alcohols by means of potassium or sodium hydroxide, more readily by moist silver oxide, which acts as silver hydroxide, according to the equation:—

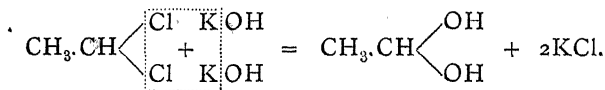


<sup>1</sup> Cf. Chap. iii. p. 33.

The corresponding aromatic compounds are not acted upon by these reagents, whilst the reaction is characteristic of all halogen compounds in the aliphatic group, although subsequent secondary changes may occasionally obliterate the direct course of the reaction. For instance, ethylidene dichloride, a dichlor-substitution product of ethane, and chloroform (trichlormethane) yield acetaldehyde and formic acid respectively, according to the equations:—

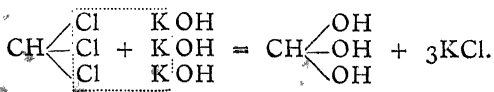


Acetaldehyde and formic acid are the final products, but there is indirect evidence to show that both reactions follow the normal course, in which each halogen atom is replaced by the univalent hydroxyl group OH, as in the case of ethyl chloride. From this standpoint the initial decompositions would be:—



Ethylidene dichloride.

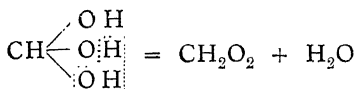
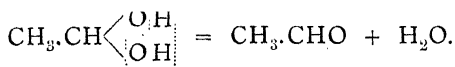
Ethylidene glycol (Intermediate compound).



Chloroform.

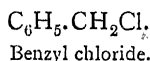
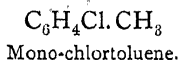
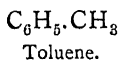
Trihydroxy-methane (Intermediate compound).

These intermediate compounds have not been isolated. Very few substances have been prepared which contain more than one hydroxyl group attached to one and the same carbon atom; when their isolation is attempted they lose one or more molecules of water to form other, more stable compounds. In this way acetaldehyde and formic acid result from the above intermediate products:—



The indirect evidence of the formation of these intermediate products consists in the fact that their derivatives have been prepared. If an alkyl group, such as methyl or ethyl, be introduced into the above molecules instead of hydrogen, to form the compounds  $\text{CH}_3\cdot\text{CH}(\text{OC}_2\text{H}_5)_2$  and  $\text{CH}(\text{OC}_2\text{H}_5)_3$  respectively, the latter are found to be stable products which can be isolated without decomposition. This increased stability is due to the weighting of the molecule by the replacement of the two or three atoms of hydrogen by the heavier ethyl groups. By analogy, it is reasonable to assume that the corresponding hydrogen compounds would be formed, as indicated in the above reactions, were it not for their want of stability; a useful method is thus available for following the course of such decompositions as are involved in the above preparations of acetaldehyde and formic acid.

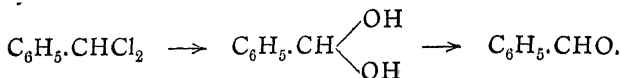
Amongst aromatic hydrocarbons, the homologues of benzene give rise to two distinct classes of halogen derivatives: those in which a hydrogen atom is substituted in the benzene ring itself, and those in which the replacement takes place in the side-chain. The isomeric monochlor-substitution products, chlortoluene and benzyl chloride are thus derived from toluene<sup>1</sup>:—



Mono-chlortoluene possesses the stability characteristic of all true aromatic haloid compounds—for instance, towards alkali—whilst its isomer benzyl chloride behaves similarly to the aliphatic halogen compounds, and yields the corresponding alcohol with potassium or silver hydroxide. The isomeric relations become more numerous when more than one hydrogen atom is replaced, but the application

<sup>1</sup> Cf. Chap. v. p. 69.

of such a reaction as the above always serves to ascertain whether one or more halogen atoms are in the ring or in the side-chain. Thus, benzaldehyde is prepared from the dichlor-substitution product of toluene, benzylidene chloride, by heating with water under pressure—a reaction exactly analogous to the preparation of acetaldehyde from ethylidene dichloride:—

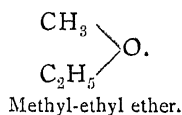
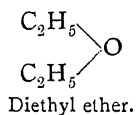
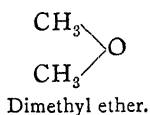


Benzylidene chloride.      (Intermediate compound.)      Benzaldehyde.

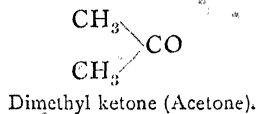
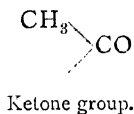
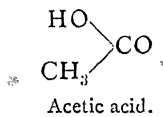
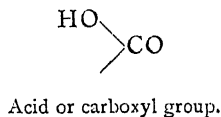
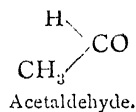
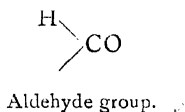
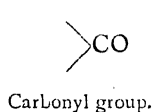
Similar differences occur in almost every group of benzene derivatives. Substituents in the ring and substituents in the side-chain have each certain distinguishing properties giving them what is known as their “aromatic” and “aliphatic character” respectively. The latter substituents are comparatively uninfluenced by the presence of the benzene ring, and they behave solely as if in combination with an aliphatic radical. Side by side with this difference in the chemical behaviour of the halogen substitution products of the aromatic hydrocarbons, there are well-defined conditions for the introduction of the halogen into the ring or into the side-chain. At the ordinary temperature and in diffused daylight the substitution takes place in the ring, whereas at the boiling-point of the hydrocarbon or in direct sunlight, side-chain substitution products result. By chlorinating cold toluene, for instance, mono-chlortoluene ( $\text{C}_6\text{H}_4\text{Cl}\cdot\text{CH}_3$ ) is first obtained; if the chlorination be continued at the boiling point, the mixed dichlor-derivative with one chlorine atom in the ring and one in the side-chain, chlorbenzyl chloride  $\text{C}_6\text{H}_4\text{Cl}\cdot\text{CH}_2\text{Cl}$  is obtained. The influence of light is somewhat less regular than that of heat; it is been made the subject of special study by Schramm.<sup>1</sup> Toluene and the three xylenes all form side-chain substitution products when treated with bromine in direct sunlight, but with mesitylene,  $\text{C}_6\text{H}_3(\text{CH}_3)_3$ , a hydrogen atom in the ring is substituted to form  $\text{C}_6\text{H}_2\text{Br}\cdot(\text{CH}_3)_3$ ; on further bromination, however, the second bromine atom enters the side-chain.

<sup>1</sup>*Berichte*, 1885, xviii. 350, 606 and 1272; 1886, xix. 212; and *J. Chem. Soc. Abstracts*, 1899, lxxvi. [1] 197.

*Derivatives of the Hydrocarbons containing Oxygen: Alcohols, Ethers, Acids, Aldehydes, and Ketones.*—Oxygen, being a divalent element, can give rise to a greater variety of combinations with the organic radicals than is possible with the univalent halogens. In direct combination with the methyl or ethyl group simple ethers such as dimethyl-ether and diethyl-ether result; if the radicals are different a mixed ether, such as methyl-ethyl ether, is possible.



Indirectly, in combination with other elements, especially hydrogen and carbon, oxygen leads to the formation of the typical groups of several most important series of compounds. Oxygen and hydrogen form the univalent group *hydroxyl*, OH; carbon and oxygen the divalent group *carbonyl*, CO. The hydroxyl group when attached to an alcohol radical group forms a saturated compound such as  $\text{C}_2\text{H}_5\text{OH}$ , ethyl alcohol. The divalent carbonyl group yields univalent groups when attached to hydrogen, to hydroxyl, or to an alcohol radical such as methyl, each of which gives rise to a stable saturated molecule when in combination with an alcohol radical, thus:—

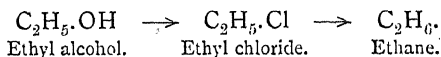


All alcohols, aldehydes, acids, and ketones contain these respective groups in combination with a hydrocarbon

radical; representing the latter by R and R', they have the following general formulæ:—

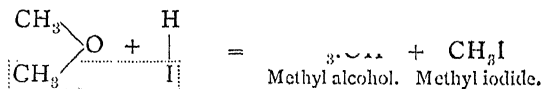


In the formula for ketones, the radicals R and R' may be either like or unlike. The structure of these groups has been proved by their chemical behaviour and by their mutual relations; similar properties are made use of for their recognition. By the action of phosphorus pentachloride, for instance, the hydroxyl group of the alcohols is replaced by chlorine, and the resulting chlorine substitution products can be reduced to their respective hydrocarbons, or obtained therefrom by direct chlorination. The relation of an alcohol to its hydrocarbon can thus be easily established, *e.g.* :—



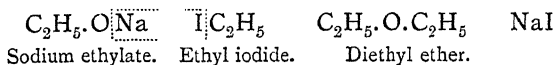
These changes prove the presence of the  $\text{C}_2\text{H}_5$ , or ethyl radical in ethyl alcohol; also, that it is attached to a univalent radical because the latter is replaceable by one atom of chlorine. This proof of the structure of the alcohols is supplemented by the reaction of ethyl chloride and its homologues with silver hydroxide, already referred to, a reaction of synthetical value because it allows of the preparation of an alcohol from its hydrocarbon.

Dimethyl ether, like ethyl alcohol, has the empirical formula  $\text{C}_2\text{H}_6\text{O}$ , but its decomposition products are entirely different and show that it does not contain an ethyl radical, but two methyl radicals, united by an oxygen atom. With hydriodic acid, for example, methyl iodide and methyl alcohol result:—



All ethers are similarly constituted; they may be regarded as alcohols in which the hydrogen of the hydroxyl group is replaced by an alcohol radical, a view that is fully justified by their synthesis. Diethyl ether, the ordinary

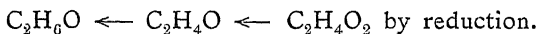
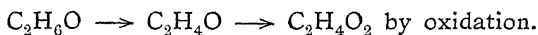
ether of commerce, is, for instance, formed when ethyl iodide is treated with sodium ethylate, according to the equation:—



This reaction and the decomposition by hydriodic acid first led Williamson (1850) to the correct formula for the ethers and to the explanation of the continuous etherification process in which ethyl ether is prepared by the action of alcohol on sulphuric acid. This method of preparation, which dates from the sixteenth century, remained unexplained until, aided by the doctrine of valency and the theory of types, Williamson was able to explain its course by his proof of the structural formula of ether.<sup>1</sup>

The structure of aldehydes, ketones, and acids has been proved by their relations to the alcohols, as well as by reactions and methods of preparation, which show a consistent variation for each group.

For instance, by the oxidation of ethyl alcohol, acetaldehyde and acetic acid are successively formed, and by means of suitable reducing agents these changes can be reversed; they are represented by the following formulæ:—



Ethyl alcohol.      Acetaldehyde.    Acetic acid.

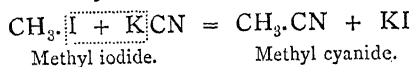
Two of the six hydrogen atoms in ethyl alcohol are removed in the oxidation. According to the structure of ethyl alcohol, which has been proved above, three of these six atoms of hydrogen are in combination with one of the carbon atoms, two with the second, and the third with oxygen in the hydroxyl group, as shown in the formula  $\text{CH}_3\cdot\text{CH}_2\cdot\text{OH}$ . An important synthetical method for the preparation of organic acids proves that the  $\text{CH}_3$ , or methyl group, is retained in acetic acid.

The univalent radical cyanogen (CN), which shows many analogies to the halogens, is readily substituted for the latter in organic compounds. By the action of

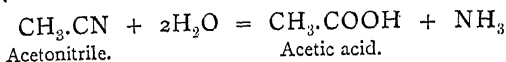
<sup>1</sup> A full account and history of the process is given by Roscoe and Schorlemmer, *Treatise on Chemistry*, 1881, vol. iii. part i. p. 323.



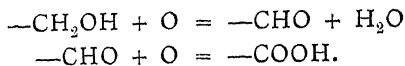
potassium cyanide on methyl iodide, for example, methyl cyanide is formed by double decomposition:—



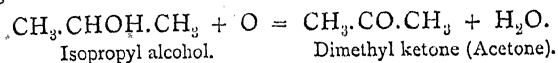
Such cyanides are decomposed by dilute alkalis or acids with the formation of organic acids and ammonia. On account of this decomposition they are more generally known as the “nitriles” of the acids obtained from them. The reaction may be represented as taking place with water:—



The presence of the methyl group in acetic acid is proved by this synthesis, and the position of acetaldehyde as the intermediate oxidation or reduction product of ethyl alcohol and acetic acid respectively, is evidence of its containing the same radical. It is, therefore, the  $\text{CH}_2\text{OH}$  group of the alcohol molecule that is attacked in the oxidation to form the aldehyde and acid groups successively:—



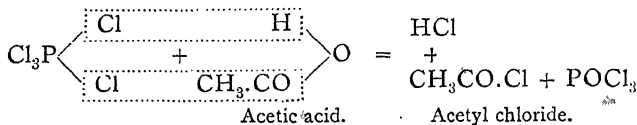
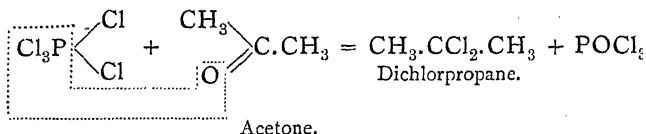
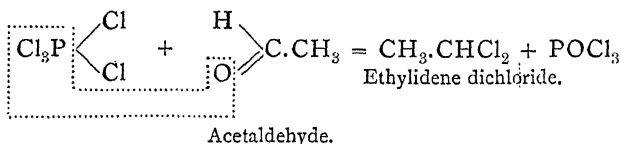
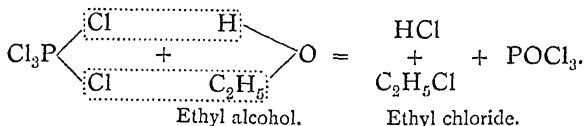
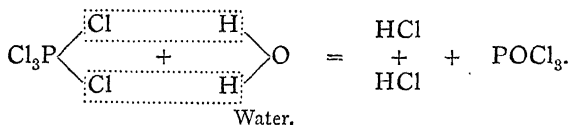
Ketones result by the oxidation of alcohols containing the  $\text{CH.OH}$  group, such as isopropyl alcohol, and they can also be proved to contain the same radicals as the original alcohol:—



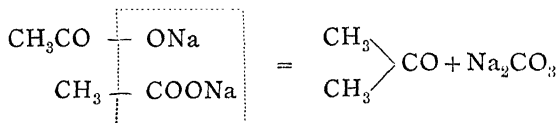
The relations of aldehydes, ketones, and acids to the alcohols are indicated by the above data; further reactions and methods of preparation are necessary to complete the proof of their structure. The action of phosphorus pentachloride on ethyl alcohol has been referred to above; this reagent also effects typical decompositions with aldehydes, ketones, and acids. In the case of ethyl alcohol the action is exactly analogous to that of the pentachloride on water; the divalent oxygen atom is displaced by two atoms of chlorine, one of which

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remains in combination with the alcohol radical, the other with hydrogen as hydrochloric acid, whilst the residue of phosphorus and chlorine combines with the liberated oxygen to form phosphorus oxychloride. The final result, therefore, is the substitution of the hydroxyl group by an atom of chlorine. With aldehydes and ketones the divalent oxygen atom of the carbonyl group is directly replaced by two chlorine atoms, without the liberation of hydrochloric acid. Acids offer the possibility of either method of interchange; they behave, however, like the alcohols which proves that they contain the hydroxyl group. These changes are represented in the following equations; the formula of phosphorus pentachloride  $\text{PCl}_5$  is written as  $\text{Cl}_3\text{P}.\text{Cl}_2$  to facilitate the comparison of the decompositions:—

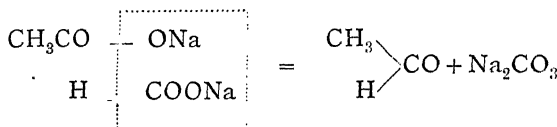


The structural relation of aldehydes and ketones shown by these reactions is confirmed by one of the readiest methods for their preparation. Ketones are obtained by distilling the salts of acetic acid or of its higher homologues, either alone or mixed in molecular proportions, whilst if sodium formate be employed with one of its homologues aldehydes result. Ketones, therefore, again appear as derivatives of the aldehydes in which a hydrogen atom is replaced by an alkyl group. These methods of preparation are typified by the following equations; they fall into line with the decomposition of the acids by heating with soda lime, an important method for the synthesis of hydrocarbons:—



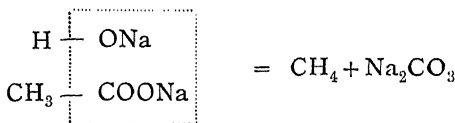
Sodium acetate (2 molecules).

Acetone.



Sodium acetate and formate.

Acetaldehyde.



Sodium acetate and soda-lime.

Methane.

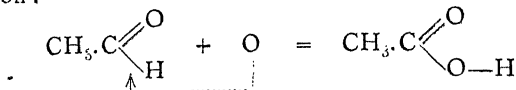
To sum up this evidence, alcohols are proved to contain the hydroxyl group by their preparation from and conversion into the monohalogen substitution products of hydrocarbons containing the same number of carbon atoms; ethers contain two alkyl radicals linked to an atom of oxygen, as proved by their decomposition with hydriodic acid and by their direct synthesis from com-

pounds in which the contained radicals are present. That aldehydes and ketones contain a carbonyl group is proved by the action of phosphorus pentachloride and by their relation to the alcohols, and finally the synthesis of acids from the halogen derivatives of the hydrocarbons *via* the nitriles and the substitution of a hydroxyl group by chlorine when they are treated with phosphorus pentachloride show that they contain the atomic grouping represented by the carboxyl radical.

In drawing conclusions as to the structure of compounds from such chemical reactions as the above, it is generally assumed that in the mutual replacement of atoms or radicals the new substituent takes the place of the one that has been removed and that it does not push itself in between any two atoms previously in direct combination. These assumptions are justified by the fact that they lead to concordant conclusions in their application to the majority of the reactions associated with the structure of compounds. Cases do certainly occur involving more than a direct replacement which at times are very misleading. They are generally conditioned by high temperatures or by violent reactions, which cause the initial product of the reaction to undergo secondary decompositions; the best check on the indirect course of such changes is usually obtained from quantitative considerations. In interpreting the value of reactions bearing on the structure of compounds, this question of yield is of great importance; if the product of a reaction only accounts for a small percentage of the original compound its formation may very likely be due to secondary decompositions. Without a full knowledge of these secondary changes, which as a rule are very difficult to follow, such reactions are valueless from a constitutional point of view. In the decompositions made use of above as evidence of the structure of alcohols and acids, a good yield of the derived product is always obtained, showing that the mass of the compound acted upon has reacted in the manner indicated by the equations. In thoroughly investigated reactions a yield of 80 or 90 per cent. is quite common. The importance of the quantitative relations in the reactions of organic compounds is quite as great as amongst inorganic substances, and, therefore, the yield

must always bear a full share of responsibility in deciding the structure of compounds.

*Autoxidation.*—The justification of the assumption that atoms and radicals replace each other directly, and do not push themselves in between atoms previously in direct combination, is not always apparent. For instance, in the equation usually given as representing the oxidation of acetaldehyde to acetic acid, the added oxygen atom enters the molecule between an atom of hydrogen and one of carbon :—



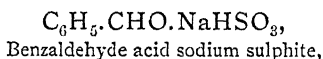
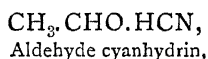
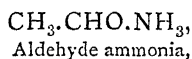
The oxidation of aldehydes to the corresponding acids takes place extremely readily, even on exposure to air at the ordinary temperature. Both inorganic and organic chemistry furnish many examples of substances that are similarly oxidised by the oxygen of the air; zinc is oxidised to oxide of zinc in presence of water, sulphuretted hydrogen to water with separation of sulphur, unsaturated hydrocarbons, especially terpenes, to oxygenated compounds the exact nature of which is at present indefinite, whilst the gradual oxidation of unsaturated acids and their glycerides, such as linseed oil, has long been made use of in the arts. The term *autoxidation* has been suggested by Traube for all oxidations that take place in this manner. These autoxidation processes were first investigated by Schönbein (1858), and have since been carefully studied by van't Hoff, Engler, Bach, Jorissen, Nef, Baeyer, Villiger and Manchot.<sup>1</sup> The object of these investigators has been to elucidate the method by which free oxygen can enter into, or change, the molecule oxidised; their experiments have revealed many important facts which bear, not only on autoxidation, but also on combustion and other methods of oxidation. The aldehydes

<sup>1</sup> Van't Hoff's work is described in his *Lectures on Theoretical and Physical Chemistry*, vol. i. p. 196; trans. by Leffeldt. Abstracts of the other papers will be found in the *Journal of the Chemical Society* from 1898 onwards; also in monographs by G. Bodländer, "Ueber langsame Verbrennung," 1899; *Sammlung chem. und chem.-technischer Vorträge*, and by C. Engler and J. Weissberg, *Kritische Studien über die Vorgänge der Autoxydation*, 1904.

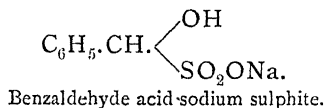
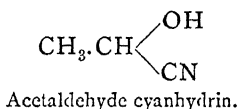
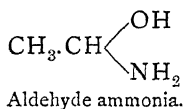
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have played an important part in the study of the subject; the application of the conclusions, as yet established, to their autoxidation will be considered after a preliminary reference to a general property of the aldehydes, which is of importance in regard to their structural relations to their oxidation products.

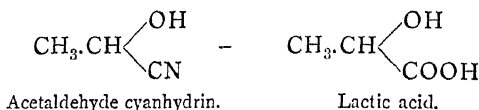
Although aldehydes and other compounds containing the carbonyl group are usually regarded as saturated molecules, it will be noticed that they contain a double linking between the carbon and the oxygen in the  $C=O$  group. By virtue of this double linking they are enabled to act, in many ways, similarly to the unsaturated carbon compounds, since, as was pointed out earlier, such double linkings form a less stable bond between the atoms than single linkings. They are thus capable of forming a number of characteristic addition products, some of which are of value for their isolation and identification. Acetaldehyde combines directly with ammonia, with acid sodium sulphite, and with hydrocyanic acid; ketones and aromatic aldehydes with the two latter reagents; acid chlorides with organic zinc and magnesium compounds, and esters with the sodium derivatives of the alcohols. The addition of these reagents, in themselves saturated molecules, is accounted for by a breaking open of the double bond between the carbon and the oxygen in the carbonyl group. The addition products:—



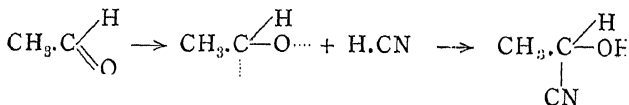
are regarded as built up as follows:—



These structural formulæ have been accepted as correct on account of the chemical behaviour of many such compounds and in part from analogy; that the cyanogen group, for instance, is present in aldehyde cyanhydrin is proved by the action of alkalis, which convert it into the carboxyl group, the characteristic reaction for the preparation of acids. This reaction forms a standard method for the preparation of such hydroxy-acids; lactic acid is thus prepared from acetaldehyde cyanhydrin, in accordance with the equation:—



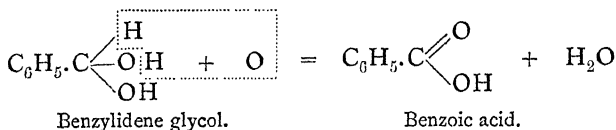
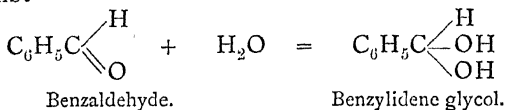
The molecular rearrangement necessary for the formation of compounds of this type is effected by the readjustment of the two bonds uniting the oxygen and carbon atom of the carboxyl group, so that they remain linked by one bond only, thus leaving a free bond with each of the atoms, to each of which a univalent atom or group can be linked. For instance, in the formation of a cyanhydrin:—



The dotted lines indicate the affinities in the unsaturated molecule, to which the added groups are attached. Many reactions receive their explanation from a readjustment of the atomic affinities in molecules, on similar lines, notably the polymerisation of aldehydes and of cyanogen compounds.

The bearing of this property of aldehydes on their oxidation, lies, in the first place, in an early idea that the reaction is conditioned by the presence of water. In the case of benzaldehyde, for instance, this addition of water allows of the formation of the unstable dihydroxy-compound, benzylidene glycol, the oxidation of which to benzoic acid, can take place by the direct removal of two atoms of hydrogen, and without the added oxygen atom pushing

itself in between the directly combined carbon and oxygen. This view, which brings the reaction into accord with the assumptions dealt with above, is expressed by the following equations:—



It will be noticed that the molecule of water added in the first equation is liberated in the second, and is, therefore, available to undergo a similar cycle of changes with another molecule of the aldehyde; hence, the smallest trace of moisture, theoretically one molecule, will suffice for the complete oxidation.

Nef states that dry benzaldehyde is not oxidised by dry oxygen, and therefore his experiment favours this view of the oxidation, but Jorissen was unable to confirm this result. It will be readily understood that it is difficult to dry a liquid like benzaldehyde so completely as to remove the last traces of water, but judging from allied changes, it is very probable that moisture favours the normal course of the oxidation.

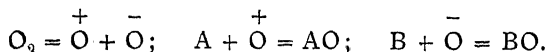
The influence of moisture on chemical change has been very fully studied amongst inorganic compounds;<sup>1</sup> it is one of the "small causes" which influence many reactions, such as the combination of hydrogen and chlorine on exposure to light, and the burning of carbon monoxide to carbon dioxide. In organic chemistry the subject has received less attention, partly on account of the greater difficulty of getting liquids and solids completely dry, as compared with gases; there is no doubt, however, that water, and similarly constituted substances such as alcohol,

<sup>1</sup> Bibliographies on the influence of moisture on chemical change are given by H. B. Baker, *J. Chem. Soc.*, 1894, lxv. 611, and by J. W. Mellor and E. J. Russell, *J. Chem. Soc.*, 1902, lxxi. 1272.



whether present as a solvent or only in traces, are most important factors in the course of many reactions.<sup>1</sup>

The recent researches on autoxidation are more far-reaching in regard to their bearing on the rationale of the oxidation of benzaldehyde. The above explanation represents the oxidation as taking place by the action of a *single oxygen atom*, whereas oxygen gas, and, similarly, that admixed with nitrogen and other gases in the air, is always looked upon as molecular. In order, therefore, that the oxidation may be effected by atomic oxygen, a previous decomposition of the molecule,  $O_2$ , is essential. Schönbein was the first to show that certain substances, such as a solution of indigo blue or of arsenious acid, which are not oxidised by molecular oxygen when alone, readily undergo oxidation in presence of an auto-oxidisable substance such as benzaldehyde, and quantitative experiments have proved that half the added oxygen goes to the aldehyde and half to the indigo or arsenious acid solution. In absence of indigo, one molecule of oxygen oxidises two molecules of benzaldehyde; in its presence only one molecule of the aldehyde is oxidised. Van't Hoff attributes this behaviour to the dissociation of the oxygen molecule into two oppositely electrically-charged atoms, one of which combines with the aldehyde and the other with the indigo blue, the *recipient* of the reaction. Representing the aldehyde by A and the recipient by B, this view of the change may be represented as follows:—



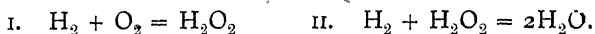
This state of dissociation is supposed to exist to some extent at the ordinary temperature; it necessitates either an electrical or a chemical difference in the two atoms of an oxygen molecule which at present lacks experimental verification.

The study of other phenomena of autoxidation has led to a more plausible explanation of the process. There is sound experimental proof that the oxidation of hydrogen to hydrogen peroxide and of sodium to sodium

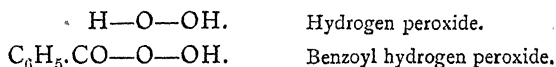
<sup>1</sup> Cf. *J. Chem. Soc.*, 1899, lxxv. 1155: Kohn and Trantom, "The interaction of Benzaldehyde and Sodium hydroxide."

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peroxide is due to molecular oxygen, and, moreover, that in the formation of their lower oxides from the elements these peroxides are similarly formed as the first product of the reaction. For instance, the combustion of hydrogen does not take place according to the usual equation:—  
 $2\text{H}_2 + \text{O}_2 = 2\text{H}_2\text{O}$ , but hydrogen peroxide is first formed, which then oxidises a second molecule of hydrogen with the formation of water, thus:—



No initial decomposition of the oxygen molecule is necessary for such a change. Similarly, in the oxidation of benzaldehyde it has been shown<sup>1</sup> that two atoms of oxygen are first added to form a peroxide, benzoyl hydrogen peroxide, the analogue of hydrogen peroxide:—



The subsequent course of the oxidation depends upon the substances present. If the aldehyde be alone, then the peroxide oxidises a second molecule and two molecules of benzoic acid result. Representing benzaldehyde by A as above:—



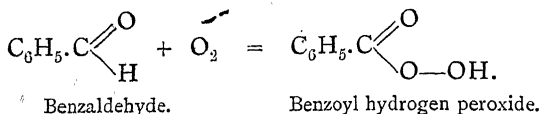
If indigo or some other recipient (B) be present, this is oxidised by the peroxide, and only one molecule of benzoic acid (AO) is formed:—



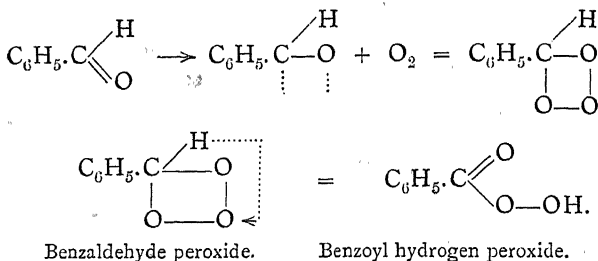
These changes are fully in accord with the quantitative relations of the reactions as established by experiment. Benzoyl hydrogen peroxide itself is a crystalline solid which dissolves in benzaldehyde; when the two compounds are mixed in molecular proportions the product changes in a few minutes to a solid mass of benzoic acid.

<sup>1</sup> von Baeyer and Villiger, *Berichte*, 1900, xxxiii. 1569.

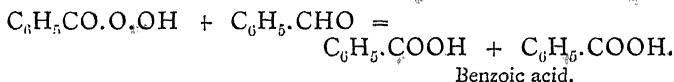
The initial oxidation of benzaldehyde can, therefore, be represented by the equation:—



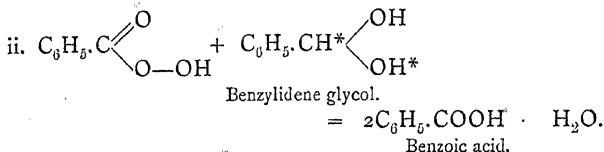
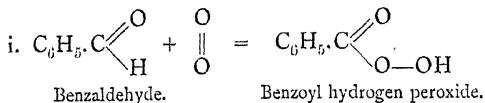
But it is more probable that the oxygen molecule is first added directly, on the lines of the aldehyde addition products referred to above, to form a peroxide of benzaldehyde, and that this passes by a molecular rearrangement into the more stable benzoyl hydrogen peroxide, thus:—



This initial product then oxidises a second molecule of benzaldehyde with the formation of two molecules of benzoic acid, just as the hydrogen peroxide formed in the oxidation of hydrogen oxidises a second molecule of the latter, as represented by the equation:—



Whether the moisture, which is probably necessary for the oxidation, plays a part in both phases of the reaction or only in one, has not been decided; if only in the second phase, then the following equations, which include the formation of benzylidene glycol, will represent the complete oxidation, the two hydrogen atoms marked with an asterisk being oxidised by an atom of oxygen from the peroxide:—



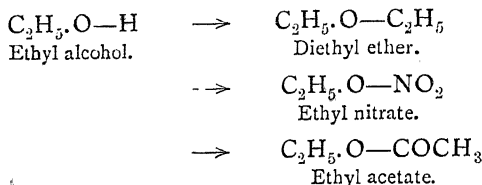
These investigations on the course of the oxidation of aldehydes bring the reaction into accord with the assumptions from which its discussion started. They, moreover, show the importance of a strict examination of those general principles which have proved the safest guide in the study of chemical changes, and of not being misled by the idea that a simple equation on paper is a full interpretation of a chemical reaction. Such equations serve a useful purpose in representing the relations of the initial and final products of a decomposition, and this justifies their use; but they often hide as much as they explain, and it is this more exact knowledge that is now being sought by chemists.

*Some Typical Derivatives of Alcohols, Acids, and Phenols.*  
—In every class of hydrocarbon derivatives certain modifications in the properties, both chemical and physical, are associated with the introduction of each substituting group or element; these lead to the formation of characteristic compounds which show a strict analogy in their chemical behaviour, modified in degree by the nature of the radical with which the substituting group or element is in combination, as also by the presence of other substituents. The derivatives of the alcohols arise from their typical hydroxyl group, the hydrogen of which is specially reactive. When treated with sodium, hydrogen is evolved and sodium ethylate formed:—



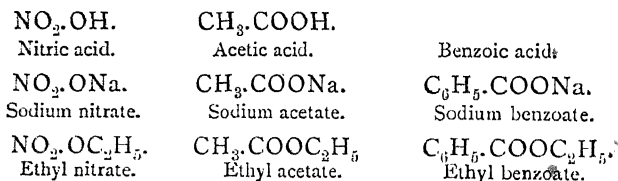
Alcohol radicals form ethers, acid radicals ethereal salts or

esters, the hydrogen of the hydroxyl group being replaced in each case, *e.g.*:—



These derivatives, in conjunction with typical reactions, such as that with phosphorus pentachloride, serve for the recognition of the hydroxyl group; if more than one hydroxyl group be present in a compound, each must fulfil these general characteristics. Glycol and glycerol, for instance, contain two and three hydroxyl groups respectively; with phosphorus pentachloride, di- and tri-chlor substitution products result. The presence of five hydroxyl groups in grape sugar and of eight in cane sugar has been proved by the preparation of their acetyl derivatives; in the former case five acetyl groups can be introduced, in the latter eight, just as the one hydroxyl of ethyl alcohol can have its hydrogen replaced by acetyl to form ethyl acetate.

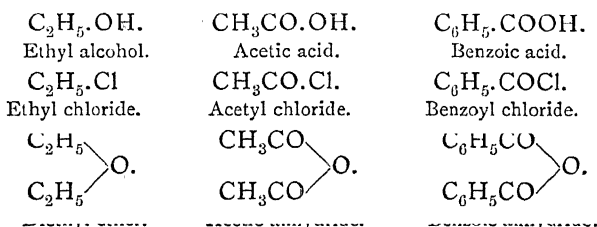
The properties of the organic acids are entirely in accord with the structure of their carboxyl group, the full importance of which, as an independent radical, was first recognised by v. Baeyer (1865). By the action of bases they form salts, exactly on the lines of the inorganic oxygen acids, and they are similarly converted into ethereal salts by their interaction with alcohols. These analogies are exemplified in the following formulæ:—



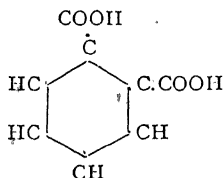
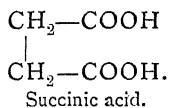
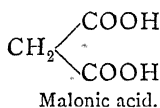
Each of these derivatives results by the replacement of the hydrogen of the hydroxyl group, just as in the case of

# DERIVATIVES OF THE HYDROCARBONS.

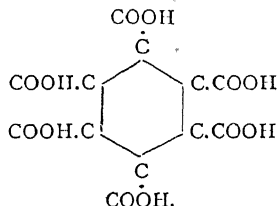
the alcohols; in the acids this group is associated with an oxygenated radical, such as *acetyl* or *benzoyl*, which is present in many other derivatives comparable with those of the alkyls, thus:—



Ethereal salts, such as ethyl acetate, which has been described as a derivative of both ethyl alcohol and of acetic acid, take one or the other position, according as they are studied from the standpoint of alcohols in which the hydrogen of the hydroxyl group is replaced by an acid radical, or as acids in which the corresponding hydrogen is replaced by an alkyl. When more than one hydrogen atom in a hydrocarbon is replaced by carboxyl, di- and polybasic acids result. Malonic acid and succinic acid are thus derived from methane and ethane respectively, phthalic and mellitic acids from benzene:—



Benzene-orthodicarboxylic acid.  
(Phthalic acid.)

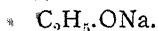


Benzene-hexacarboxylic acid.  
(Mellitic acid.)

As a dibasic acid, like sulphuric acid, succinic acid can form two series of salts and esters, according as one or

both of its typical hydrogen atoms are replaced; similarly, all the other typical reactions of the acids are reproduced by each of the carboxyl groups present in a compound. When succinic acid is completely neutralised by a base, such as sodium hydroxide, the neutral sodium succinate  $C_2H_4(COONa)_2$  is formed. Since the basicity of an organic acid is represented by the number of carboxyl groups present, the latter factor can be determined, in a compound of known molecular weight, by neutralisation with alkali, employing the usual methods of either volumetric or gravimetric analysis. Purely physical methods can also be made use of for the same purpose; of these the determination of the electrical conductivity is the most important.<sup>1</sup>

The hydrogen of the hydroxyl group, both in alcohols and acids, can be replaced by sodium and other metals, as stated above, but the properties of the resulting compounds, such as sodium ethylate and sodium acetate, are very different.

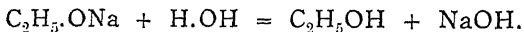


Sodium ethylate.



Sodium acetate.

The former is completely decomposed or hydrolysed by water into ethyl alcohol and sodium hydroxide according to the equation:—



It cannot, accordingly, exist in aqueous solution, nor are the higher homologues of ethyl alcohol, such as amyl alcohol, which are insoluble in water, dissolved by aqueous alkalis, thus showing that they do not form salts in aqueous solution. Their sodium derivatives are, therefore, not regarded as true salts. The properties of sodium acetate, on the contrary, are quite analogous to those of the salts of the inorganic acids, and benzoic acid, which is only slightly soluble in water, is readily dissolved by dilute alkalis; such salts are quite stable in solution, and regenerate the free acid only on the addition of an acid sufficiently strong to liberate the acid in question from its salt. The oxygenated radicals of the organic acids have all a similar acidifying influence on the hydroxyl group; the resulting compounds

<sup>1</sup> The method is described in text-books on *Physical Chemistry*.

$$\text{C}_6\text{H}_5.\text{OH} + \text{NaOH} = \text{C}_6\text{H}_5.\text{ONa} + \text{H}_2\text{O}$$

Phenol.                      Sodium phenate.

*Derivatives of Unsaturated Hydrocarbons.*—Whilst each separate substituent of a hydrocarbon confers a certain definite chemical character on the containing molecule, the



properties and behaviour of the latter are modified by its degree of saturation, as well as by the mutual influences of dissimilar substituents and by the molecular position of the substituting group or groups.

Unsaturated alcohols, aldehydes, and acids are known bearing the same relation to the saturated compounds that ethylene and acetylene do to ethane. Phenol and benzoic acid are derivatives of unsaturated cyclic hydrocarbons, and their addition products, like those of benzene, lead to saturated cyclic compounds of the hexamethylene type.

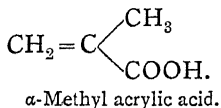
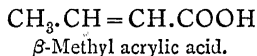
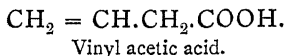
The general characteristics of unsaturated aliphatic and cyclic substances are respectively repeated in their derivatives; an unsaturated aliphatic alcohol forms esters, and is prepared from its chloride in the usual way, but it possesses, in addition, the power of taking up one or more molecules of bromine or of hydrobromic acid, according to its degree of unsaturation. This latter property occasionally necessitates a circuitous route for the preparation of a derivative, but as a general rule the most direct way to unsaturated substances is from saturated compounds. The most interesting problem associated with the derivatives of unsaturated hydrocarbons is the determination of the position of their double or triple links. Von Baeyer's work on this subject, and its bearing on the structure of benzene, has already been referred to; amongst aliphatic compounds the matter has been the subject of important investigations in connection with the unsaturated acids.

The simplest unsaturated acid, acrylic acid, is derived from ethylene by the replacement of one hydrogen atom by the carboxyl group, and there is obviously only one possible position for the double bond:—

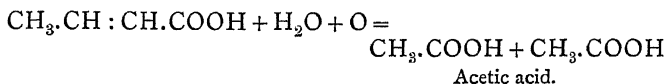
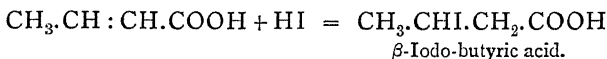
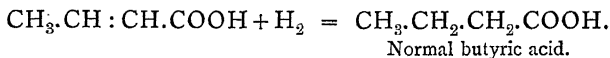


The next homologue of the series has the formula  $\text{C}_4\text{H}_6\text{O}_2$ , and no less than four different structures are possible for an acid of this composition, three of which are unsaturated; the fourth is a saturated cyclic acid, trimethylene carboxylic acid. Since each of the three contains the carboxyl group,  $\text{COOH}$ , they must differ in

the structure of the residue  $C_3H_5$  with which this is combined; the following are theoretically possible formulæ for these isomers:—

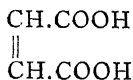


Three unsaturated acids of the above composition have been known for a long time, and with three possible formulæ available, it should not have been difficult to assign them their respective structures. But the task proved far less easy than might have been anticipated, although the structure of the last,  $\alpha$ -methyl acrylic acid, had been satisfactorily established by a simple synthesis. The two remaining acids are found in croton oil (the oil of *Croton tiglium*), and are known as crotonic and isocrotonic acid. Crotonic acid is a crystalline solid which melts at  $72^\circ$ , isocrotonic acid a liquid boiling at  $172^\circ$ , and which is not solidified even at  $-15^\circ$ . These marked differences in physical properties show, of course, that the acids cannot possibly be identical, and still they behave so similarly in their chemical reactions that it is difficult to justify different structural formulæ for them. This similarity is especially obvious in their addition products with the halogens and halogen acids and in the action of oxidising agents. Crotonic acid, for instance, yields normal butyric acid on reduction,  $\beta$ -iodo-butyric acid with hydriodic acid and two molecules of acetic acid when oxidised by fusion with an alkali hydroxide. These reactions justify the acceptance of the  $\beta$ -methyl acrylic acid formula, thus:—

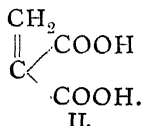


The vinyl acetic acid formula remains for isocrotonic acid, but in its reactions with the above reagents it yields identically the same results as crotonic acid. Some of these are theoretically possible, but are so much out of accord with the behaviour of other compounds constituted similarly to vinyl acetic acid, that if this structure be assigned to isocrotonic acid, it must be regarded as abnormal in the most characteristic reactions of analogous unsaturated compounds. Were no alternative structure possible, some explanation of the abnormal behaviour of isocrotonic acid would have to be sought, and many inconclusive experiments were made with this object until the modern developments of stereochemistry provided a new key to the isomerism which has proved well in accord with the chemical behaviour of the two acids. The stereochemical relations of these acids will be dealt with in Chapter XII., and it will be seen that they afford a very satisfactory explanation of their reactions. The possibility of one of them being built up on the vinyl acetic acid formula has been now completely disproved by the preparation of a new acid which, from its synthesis and decomposition<sup>1</sup>, has been definitely shown to have this structure.<sup>1</sup>

In a very similar way, all synthetical methods of preparation have failed to show any difference in the linking of the atoms in maleïc and fumaric acids. Both are unsaturated dibasic acids having the empirical formula  $C_4H_4O_4$ . Fumaric acid, which is found somewhat widely distributed in the vegetable kingdom, occurring in Iceland moss, truffles and in several species of *Fumaria*, is a crystalline substance sparingly soluble in water. Maleïc acid, on the contrary, is very soluble in water, and does not occur in any natural products. Subtracting the two carboxyl groups,  $2(COOH)$ , from the formula  $C_4H_4O_4$ , a residue,  $C_2H_2$ , remains which leads to the two following, possible structural formulæ for the acids:—



and



I.

II.

<sup>1</sup> Cf. J. Wislicenus, *Berichte*, 1899, xxxii., 2047; and Fichter and Sonneborn, *Berichte*, 1902, xxxv., 938.

## DERIVATIVES OF THE HYDROCARBONS.

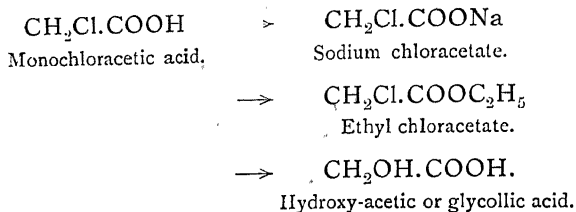
In the formation of addition products both fumaric and maleïc acid behave as if built up on Formula I.; their decomposition products, though not always identical, are also out of accord with the second formula for either of the two acids. Moreover, both the free acids and their derivatives are characterised by the ease with which they can be mutually transformed; a trace of hydriodic acid, for instance, suffices to convert a practically unlimited quantity of maleïc acid into fumaric acid, and it has been recently shown that the same change may be effected by platinum black,<sup>1</sup> whilst the anhydride of maleïc acid is formed when fumaric acid is heated. These changes take place so readily that it is unlikely such a molecular rearrangement as would be necessary for a compound of the first formula to pass into one of the second, or vice versa, could occur under these conditions. There is other important evidence in favour of accepting Formula I. as representing the structure of both fumaric and maleïc acid; as in the case of the crotonic acids, stereochemistry has furnished the necessary explanation of their isomerism.<sup>2</sup>

The study of the structure of unsaturated compounds, which is essentially concerned with the position and function of the multiple linkings, has thus led to one of the most important developments of the conditions of atomic linkage, the stereochemistry of the unsaturated compounds.

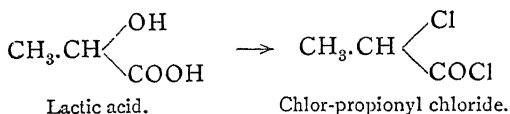
*Derivatives of the Hydrocarbons containing Dissimilar Substituents.*—When two or more hydrogen atoms in a hydrocarbon are replaced by dissimilar substituents, each substituting group or atom retains its characteristic properties, and its presence may be recognised by typical reactions such as those already considered in the case of alcohols, acids and the haloid derivatives of the hydrocarbons. For instance, chloracetic acid yields salts and esters like acetic acid, whilst the presence of the halogen is shown by the action of silver hydroxide when it is replaced by hydroxyl to form a hydroxy-acid, just as ethyl chloride yields ethyl alcohol:—

<sup>1</sup> Loew and Asō, *Bull. Coll. Agr. Tokyo*, 1906, 1.

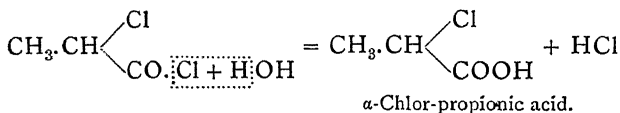
<sup>2</sup> Cf. Chap. xii. p. 306.



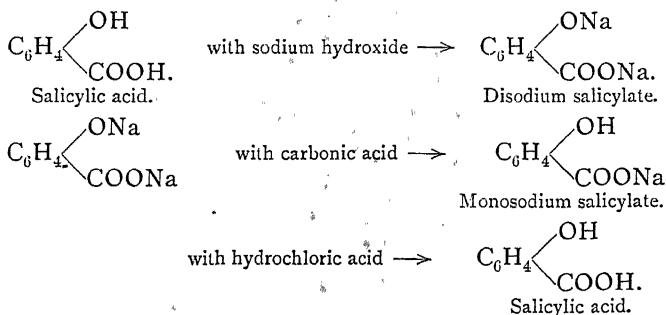
Hydroxy-acids, which include some of the most important and widely distributed acids of the vegetable kingdom, such as malic, tartaric, citric and salicylic, give the characteristic reactions of both alcohols and acids. When lactic acid, hydroxy-propionic acid, is treated with phosphorus pentachloride both the alcohol, and carboxyl, hydroxyl groups are replaced by chlorine to form chlor-propionyl chloride thus:—



These two chlorine atoms are at once differentiated by the action of water; the carboxyl chlorine alone is hydrolysed, like that of acetyl chloride, the second chlorine atom, which is analogous to that of ethyl chloride, being un-attacked. The resulting product is, therefore, a halogen acid:—

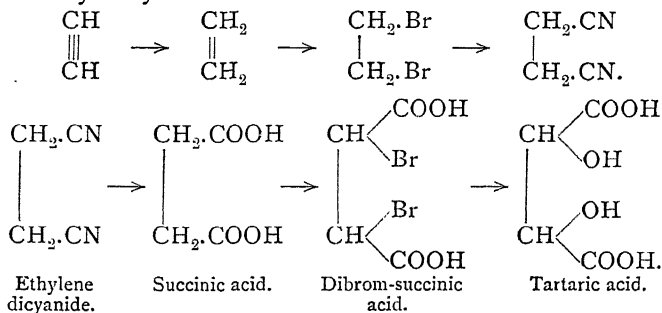


Again, salicylic acid, a hydroxy-benzoic acid, is converted into a di-sodium salt by treatment with sodium hydroxide; carbonic acid removes one only of the sodium atoms, a mineral acid is required to remove the second. A reference to the behaviour of the sodium salts of phenol and of benzoic acid will at once indicate the bearing of these decompositions on the structure of salicylic acid:—



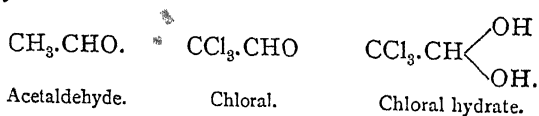
The preparation of these mixed compounds is usually effected by means of the general methods for each substituting group; there are, however, several special reactions by means of which two different substituting groups are simultaneously introduced, such as the preparation of lactic acid from acetaldehyde,<sup>1</sup> which affords, in addition, a good proof of the structure of the acid.

Tartaric acid is obtained from succinic acid by first replacing two hydrogen atoms in the latter by bromine, and then treating the dibrom-substitution product with silver hydroxide; since succinic acid can be obtained from acetylene *via* ethylene, its dibromide, and dicyanide, the synthesis of tartaric acid, starting from the elements carbon and hydrogen, can thus be effected. The stages in these changes are represented below; the reactions carry with them the proof of the structural formula of tartaric acid as dihydroxy-succinic acid:—

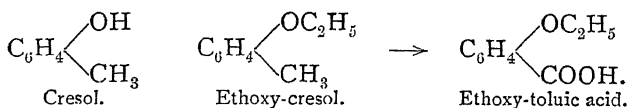


<sup>1</sup> Cf. this chapter p. 138.

The influence of dissimilar substituents on the properties of the containing molecule, as a whole, follows essentially from their typical properties and from their electro-chemical character. The halogen fatty acids are stronger acids than the simple acids, and the acidity increases with the number of halogen atoms introduced, a property due to the electro-negative character of the substituent. Similarly, whilst phenol has been characterised as a very weak acid, trichlor-phenol decomposes the alkali carbonates. As is to be expected, such electro-negative substituents have a weakening influence upon any bases into which they are introduced. Thus, the chlor-anilines are very much weaker bases than aniline itself. The nitro-group has a still more pronounced electro-negative influence than a chlorine atom. Such substituents also increase the stability of certain compounds, typically the addition products of the aldehydes. The instability of compounds in which two hydroxyl groups are attached to one and the same carbon atom has already been referred to; analogous compounds containing halogen atoms are more stable and can be isolated. Chloral, for instance, the trichlor-substitution product of acetaldehyde, combines with water to form the valuable hypnotic, chloral hydrate, in which the two hydroxyl groups are undoubtedly present, because the hydrate does not give certain characteristic reactions of aldehydes, which it would do were the added water simply present as water of crystallisation.

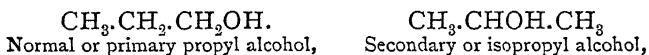


An interesting molecular influence of the hydroxyl group occurs amongst aromatic compounds. Whereas all homologues of benzene are readily oxidised to carboxylic acids—toluene, for instance, to benzoic acid—the introduction of the hydroxyl group inhibits this oxidation by acid oxidising agents, such as chromic acid. When, however, the hydrogen of the hydroxyl is replaced by an alkyl or acid radical the oxidation proceeds as usual; thus, cresol does not yield toluic acid, but its ethyl ether forms the corresponding toluic acid derivative:—

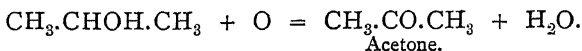


The number of mixed derivatives of the hydrocarbons is naturally far in excess of those containing like substituents only; their preparation and the recognition of the various substituting groups present no great difficulties in the case of the simpler hydrocarbons. But amongst more complex products, and especially when the substituents are not only different but also numerous, the mutual influences exerted are more difficult to follow, and the investigation of the structure of a complex molecule may thus become a very formidable problem.

*The Influence of the Molecular Position of Substituents on the Properties of Compounds: Steric Hindrance.*—The properties and chemical behaviour of organic compounds, in addition to being modified by the presence of dissimilar substituents, are also influenced by the position of the substituting groups or elements in the molecule. This factor has already been illustrated in the oxidation products of the alcohols; ethyl alcohol first forms an aldehyde, isopropyl alcohol, a ketone. The two isomeric propyl alcohols:—



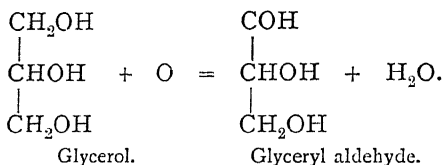
are both derived from propane by the replacement of one hydrogen atom by hydroxyl. They yield sodium compounds, esters, and ethers possessing similar properties to the corresponding derivatives of ethyl alcohol, and the presence of the hydroxyl group is recognised by the general reactions with phosphorus pentachloride or with acetyl chloride. In addition to these common properties, however, they show a difference in their behaviour towards oxidising agents. The normal or primary alcohol forms an aldehyde, just as ethyl alcohol does, whilst isopropyl alcohol forms acetone, in accordance with the equations:—



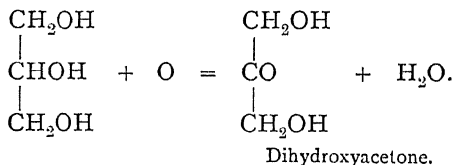


These changes are reversed by the action of reducing agents. On further oxidation the aldehyde yields propionic acid, whilst the ketone is broken up with the formation of acids, none of which contain as many carbon atoms as the original alcohol. Similar differences obtain between all primary and secondary alcohols, and are due to the difference in the molecular position of the substituting group. In primary alcohols the hydroxyl is attached to the end carbon atom of the chain, forming the group  $\text{CH}_2\text{OH}$ , in secondary alcohols to an intermediate carbon atom, as  $\text{CH.OH}$ ; or, in the one case the hydrogen of a  $\text{CH}_3$  group, in the other that of a  $\text{CH}_2$  group, has been replaced by hydroxyl.

Glycerol is a tervalent alcohol containing two primary and one secondary alcohol groups; its initial oxidation product might, therefore, be either an aldehyde-alcohol or a ketone-alcohol, thus :—



or :—



As the result of experiment it has been found that both products may result simultaneously, though by modifying the conditions of oxidation a preponderance of one or of the other can be secured; both are of interest, on account of their having served as the starting-point in one of the first syntheses of the sugar group.<sup>1</sup>

Radicals containing carbon, such as carboxyl, similarly induce variations in the presence of a second substituent, either like or unlike. Such variations are to be observed

<sup>1</sup> Cf. Chap. xiii. p. 335.

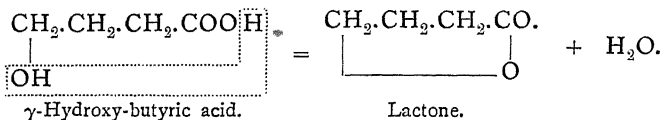
amongst dibasic acids, halogen acids, hydroxy-acids, diketones and ketonic acids, and differences in stability, as well as in chemical character, are associated with the molecular position of the substituting groups. Thus, of the three hydroxy-acids derived from butane and named  $\alpha$ ,  $\beta$ , and  $\gamma$  hydroxy-butyric acid respectively, according to the proximity of the hydroxyl group to the carboxyl at the end of the chain, the  $\alpha$  acid is the most stable.

$\text{CH}_3.\text{CH}_2.\text{CHOH}.\text{COOH}.$   $\alpha$ -Hydroxy-butyric acid.

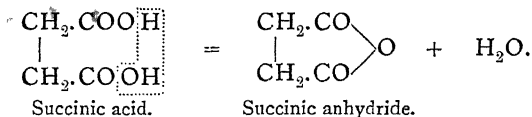
$\text{CH}_3.\text{CHOH}.\text{CH}_2.\text{COOH}.$   $\beta$ -Hydroxy-butyric acid.

$\text{CH}_2\text{OH}.\text{CH}_2.\text{CH}_2.\text{COOH}.$   $\gamma$ -Hydroxy-butyric acid.

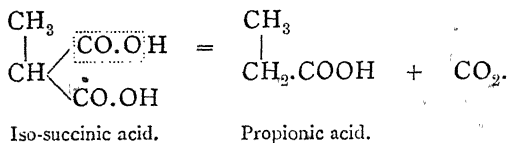
Upon heating they all lose a molecule of water, but each in its own way, and this behaviour is similar for all analogous compounds. The  $\alpha$ -acid forms a rather complex double anhydride, the  $\beta$ -acid an unsaturated acid, and the  $\gamma$ -acid a simple or internal anhydride, known as a lactone. This last decomposition, which is represented by the following equation, is of interest because the stereochemical relations of the contained carbon atoms explain why this change occurs with the  $\gamma$ -acid and not with the other two isomers<sup>1</sup>:—



Differences in chemical behaviour also occur, on similar lines, when like substituents only are present. Thus, while succinic acid readily forms an anhydride from which the free acid can be regenerated, its isomer, iso-succinic acid, in which the two carboxyl groups are attached to the same carbon atom, does not, but on heating, it loses a molecule of carbon dioxide to form a monobasic acid:—



<sup>1</sup> Cf. Chap. xii. p. 313.



Analogous examples abound amongst all derivatives of the aliphatic hydrocarbons; they have been recognised by the investigation of the chemical behaviour of similarly constituted molecules, and now serve as a valuable guide in drawing conclusions as to the relative position of substituting groups.

Amongst aromatic compounds the influence of the relative position of the substituting groups only comes into play when more than one substituent is present, owing to the symmetry of the benzene ring. It is evident in the relative properties of many di-substitution products of benzene<sup>1</sup> and in the empirical laws of substitution of benzenoid compounds.<sup>2</sup> Also, a number of extremely interesting instances of this influence have been brought out by the studies of Victor Meyer and his pupils on the properties of certain substituted benzoic acids and their derivatives, which have since been extended by other investigators.<sup>3</sup>

When the two hydrogen atoms next to the carboxyl group in benzoic acid are replaced, for instance, by bromine, the dibrombenzoic acid no longer possesses the power, common to other organic acids, of forming a methyl ester when treated with methyl alcohol in presence of hydrochloric acid<sup>4</sup>; if, however, the two substituting bromine atoms are in a different position, the acid behaves normally. Thus, of the two acids formulated below, the first is not esterified, whilst the second is, although they

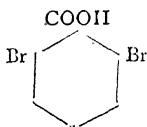
<sup>1</sup> Cf. Chap. x. p. 214.

<sup>2</sup> Cf. Chap. x. p. 215.

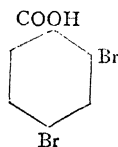
<sup>3</sup> Cf. V. Meyer, *Berichte*, 1894, xxvii. 510, 1580, 3140; 1895, xxviii., 182, 1254; 1896, xxix. 830. Lloyd and Sudborough, *J. Chem. Soc.*, 1899, lxxv. 580. W. Davis, *J. Chem. Soc.*, 1900, lxxvii., 33.

<sup>4</sup> Chap. ix. p. 168. Cf. also a monograph, "Über den Einfluss der Kern-substitution auf die Reaktionsfähigkeit aromatischer Verbindungen," Julius Schmidt, 1902, *Sammlung chem. und chem.-technischer Vorträge*.

differ only in the relative position of the two atoms of bromine :—



Dibrombenzoic acid.

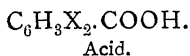


Dibrombenzoic acid.

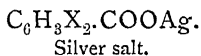
[COOH : Br : Br = 1 : 2 : 6]

[COOH : Br : Br = 1 : 2 : 4].

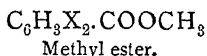
A similar inhibiting influence is produced by the groups  $\text{CH}_3$ ,  $\text{OH}$ ,  $\text{COOH}$ ,  $\text{F}$ ,  $\text{Cl}$ ,  $\text{Br}$ ,  $\text{I}$ , and  $\text{NO}_2$ , either separately or in conjunction with each other, when they occupy the position of the two bromine atoms in the first of the above formulæ. Ethereal salts of such di-ortho-substituted benzoic acids can, however, be prepared indirectly, by first converting the acid into the silver salt and then treating this with methyl iodide, the silver which replaces the hydrogen of the carboxyl being substituted by the alkyl group, as represented in the following formulæ, in which  $\text{X}_2$  indicates the two ortho-substituents :—



Acid.



Silver salt.

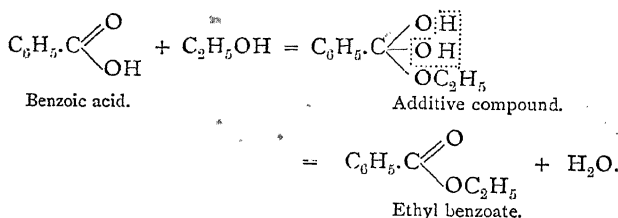


Methyl ester.

The esters obtained in this way are far more difficult to decompose than those in which the ortho-positions are not substituted; it is thus seen that the very conditions of substitution which inhibit the reactivity of the acids exert a protective influence over their esters. Other acid derivatives, such as the acid chlorides, amides, and nitriles, are similarly protected by ortho-substituents.

Many analogous instances of the inhibiting influence of neighbouring groups have been observed in the reduction of nitro-compounds to amines, in the action of alcohols upon acid chlorides, and in the preparation of acetyl and of benzaldehyde derivatives of aromatic bases. The term *steric hindrance* has been introduced to express this inhibiting or retarding influence of substituents on the reactivity of a substance, since it is regarded as largely due to the spatial position occupied by the substituting groups. It has been suggested by Wegscheider (1895)

that this effect is due to the initial formation of an additive compound of the alcohol and the acid, in the case of esterification, which subsequently decomposes into the ester and water; the presence of substituents in proximity to the carboxyl group he regards as preventing or retarding the formation of such additive compounds, on account of the space the substituents must necessarily occupy. The formation of the intermediate additive compound depends on the breaking of the double bond between the carbon and oxygen of the carboxyl group, as in the case of aldehydes, and may be represented as follows for the formation of ethyl benzoate;—



This view is fairly in accord with many of the observed data on steric hindrance, but not with all, and until more is known of the manner in which the atoms of a molecule fill the space occupied by the latter, the real explanation of steric hindrance is not likely to be ascertained.

## CHAPTER IX.

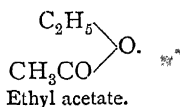
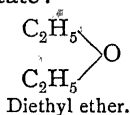
### ETHEREAL SALTS.

The relation of ethereal salts or esters to ethers—Natural occurrence and uses of ethereal salts.

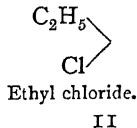
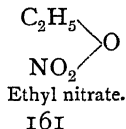
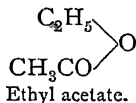
The preparation of ethyl acetate—The action of mass—Reversible or balanced reactions—The saponification of ethereal salts—The hydrolysis of ethereal salts by mineral acids—Catalysis.

Some synthetical applications of ethereal salts:—Diethyl malonate, Ethylacetoacetate—The structure of the sodium derivatives of ethylacetoacetate and of diethyl malonate.

THE derivatives of the organic acids in which the hydrogen of the carboxyl group is replaced by an alcohol radical, such as methyl or ethyl, are known as *Ethereal Salts* or *Esters*. Their relation to both acids and alcohols has been exemplified in the previous chapter in the case of ethyl acetate; this relation is typical of all ethereal salts. The analogy in structure between ethers and ethereal salts is shown by comparing the formulæ of diethyl ether and of ethyl acetate:—



Both contain two radicals united to the divalent oxygen atom, the second alkyl radical of the ether, in the case of the ester, being replaced by an acid radical. Similar derivatives of inorganic acids are known, amongst which the halogen derivatives of the hydrocarbons may be included as the ethereal salts of halogen acids:—



The term "Ester" was introduced by Gmelin in view of this analogy between these derivatives of acids (German, *Säure*) and ethers, and it has been usefully adopted in this country as an equivalent of "Ethereal salt."

*Natural occurrence and uses of Ethereal Salts.*—These compounds are of interest and importance from many points of view. Organic acids are very frequently found in plants, in combination with alcohols, as ethereal salts; thus, Gaultheria oil—the oil of *Gaultheria procumbens*—is the methyl ester of salicylic acid; many of the simpler fatty acids, such as butyric and valeric acids, occur in plants as esters as well as in the free state; bees' wax, Chinese wax, and spermaceti are all simple esters of the higher fatty acids, and the naturally occurring fats and oils are compounds of the trivalent alcohol, glycerol, with palmitic, stearic, and oleic acids. A similar condition of combination results from certain metabolic changes in the animal body. Phenol, when taken internally, is eliminated as an ester of sulphuric acid, and a similar derivative of indoxyl, a compound of the indigo group, is found in the urine of herbivora, especially after treatment with indole. In the synthetical preparation of many compounds, ethereal salts have proved of the utmost value. They are themselves readily accessible, and, therefore, a convenient and economical starting point. These syntheses have been realised both amongst aliphatic and cyclic compounds, and have, in addition, served for the preparation of the latter from the former; further, the simpler esters lead readily to the preparation of other more complex compounds, such as ethylacetate, the study of which has led to important developments of modern organic chemistry.

The ethereal salts of the organic acids have served a still more valuable purpose in the investigation of the influence of concentration in chemical change and in the relative measurement of the chemical affinity of acids and bases; the conditions of formation and decomposition of the esters render them specially suitable for the study of these fundamental problems of chemical dynamics.

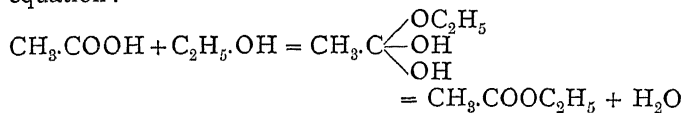
The technical application of the esters completes the record of their use. In the form of glycerides they are the chief raw material in the soap industry and in the manufacture of candles; some of the simpler aliphatic esters are

## ETHEREAL SALTS.

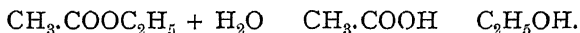
employed in perfumery and in pharmacy, whilst gun cotton, nitroglycerine, and celluloid are derived from ethereal salts of nitric acid.

The aim of the present chapter is to study the conditions of formation and decomposition of ethereal salts and their value for the synthetical preparation of compounds, together with certain important considerations that have arisen from the investigation of these changes.

*The Preparation of Ethyl Acetate: the Action of Mass: Reversible or Balanced Reactions.*—The simple relation of ethyl acetate to the alcohol and acid from which it is derived is shown by its preparation from these constituents. When acetic acid and ethyl alcohol are heated together in molecular proportions, the ester is formed, with the separation of water, as shown in the equation given below. It appears probable that the first action of the alcohol upon the acid is to form an addition compound,<sup>1</sup> which immediately eliminates water according to the equation:—



The theoretical yield of ethyl acetate, according to this equation, would be 88 grams for every 60 grams of acetic acid and 46 grams of ethyl alcohol used for the preparation, these quantities representing the respective molecular weights of the substances concerned. But, as a matter of fact, when these molecular proportions of acid and alcohol are employed the yield never exceeds two-thirds of this amount. The reaction is always incomplete, about one-third of the alcohol and of the acid remaining apparently unchanged. If, on the other hand, the products of the reaction, ethyl acetate and water, are heated together in molecular proportions, ethyl alcohol and acetic acid are formed according to the equation:—



and this decomposition also reaches a limit when approximately one-third of the ester has been converted into

<sup>1</sup> Cf. Chap. viii. p. 160.



alcohol and acid. The reaction can, therefore, proceed in either direction, and whether it be started from the acid and alcohol, or from the ester and water, the same condition of equilibrium is reached between the four reacting substances—alcohol, acid, ester and water. It is this condition that limits the change in the preparation of ethyl acetate from molecular proportions of ethyl alcohol and acetic acid; the equilibrium is not to be regarded as involving a stationary condition of the reacting substances, but rather a “balanced action” in which the molecules of the ester are formed and decomposed with the same velocity.

It is customary to represent such *reversible* or *balanced reactions* by equations in which the ordinary sign of equality is substituted by oppositely directed arrows, e.g. :—



A similar equilibrium obtains in the preparation of all esters from molecular proportions of alcohol and acid, and the limit of esterification is almost independent of the chemical nature of the acid or alcohol employed.

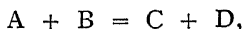
Such balanced reactions are by no means restricted to the preparation of esters; numerous other instances are known both amongst organic and inorganic substances, and the results obtained have served to establish the important influence of *mass* or *concentration* in all cases of chemical change. The view that chemical affinity is the sole determining cause of the course of a chemical change was first challenged by Berthollet (1803), who put forward the opinion that it is primarily the relative concentrations of the reacting substances, in conjunction with such properties as solubility and volatility, that direct chemical changes, and that chemical affinity plays only a secondary part. This view received practically no support for many years, but the investigations of Berthelot and Péan de St. Gilles (1862) on esterification, followed by the more exact studies of Guldberg and Waage (1867), have shown that although Berthollet somewhat exaggerated the influence of concentration, his contention was in the main correct, and that this factor, together with tem-

perature, time and other conditions, must always be considered in judging of the relative affinities of elements or their equivalents. The law of *mass action*, founded by Guldberg and Waage, has received abundant confirmation from subsequent investigations, and has been one of the most fruitful generalisations in the whole of chemistry.

The formation of the ethereal salts of the organic acids has been a specially convenient means of studying the influence of mass, because the reaction can be readily carried out at a constant temperature and without any change of state amongst the reacting substances, such as the separation of any one product in an insoluble form, which would remove it from the sphere of action. Further, because the reaction proceeds sufficiently slowly towards the limit to permit an analytical examination of the products at different time intervals during the change; the connection between the rate of the reaction and the amount of the reacting substances can thus be followed. This connection is of fundamental importance in all chemical changes.

In a mixture of two substances, the molecules of which are, according to the kinetic theory, in continual motion, the rate at which they will react is obviously proportional to the frequency with which the molecules come in contact with each other. This is, in its turn, proportional to the number of molecules of each which are present in a given volume. It is customary to speak of the number of gram-molecules per litre as the *molecular concentration* or *active mass* of a compound. The experiments of Guldberg and Waage fully confirmed this view, and led them to the conclusion that the velocity of chemical action is always proportional to the active mass of each of the reacting substances. Its application can first be advantageously considered in the case of a non-reversible reaction.

Suppose that by the action of one molecule of a substance A, on one molecule of a substance B, single molecules of substances C and D are formed, according to the equation:—



and that the molecular concentrations of A and B are *a* and *b* respectively, then the velocity of the reaction will,

according to Guldberg and Waage, be proportional to both  $a$  and  $b$ , and, therefore, to the product  $ab$ , and will be equal to this value multiplied by a constant. The constant will depend upon the specific reaction concerned; it represents the velocity at which the reaction will proceed when the reacting substances are of unit molecular concentration. It is called the *velocity constant* of the reaction, and is usually denoted by  $k$ . In the start, the velocity of the above reaction will be represented by the equation:—

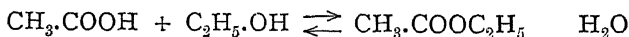
$$\text{Velocity} = ab \times k.$$

As the reaction proceeds, the concentrations of A and B will decrease, and if, after a certain time ( $t$ ), they have diminished by  $x$  gram-molecules per litre, owing to the formation of  $x$  molecules of C and of D, the velocity of the reaction will be correspondingly decreased, and will be represented by the equation:—

$$\text{Velocity}_t = k(a-x)(b-x),$$

and so the reaction will proceed, at a continually decreasing rate, until one or other of the substances A or B has completely disappeared. The velocity constant  $k$ , which represents the affinities of the reacting substances under the conditions of the experiment, remains the same throughout, the change in velocity being only influenced, as the reaction proceeds, by the decrease in the molecular concentrations or active masses of A and B.

In the formation of an ethereal salt there are two velocity constants to consider, owing to the reversibility of the reaction. If the molecular concentrations of the four substances in the equation:—



are represented by  $a$ ,  $b$ ,  $c$ , and  $d$  respectively, the velocity constant of the direct action by  $k$ , and that of the reverse action (decomposition of the ester into alcohol and acid) by  $k'$ , then the respective velocities, after the formation of the ester has begun will be:—

$$\text{Velocity of direct action} = k \times ab.$$

$$\text{Velocity of reverse action} = k' \times cd.$$

After a certain time a condition of equilibrium will be reached, which means, as already stated, that the reaction proceeds with equal velocities in both directions; this condition must obviously be represented by the equation:—

$$k \times ab = k' \times cd.$$

If molecular proportions of ethyl alcohol and acetic acid are used, then  $a=b$ ; and since molecular proportion of ester and water are then formed in the reaction,  $c=d$ . Supposing  $x$  gram-molecules of acid and of alcohol have been converted into ester and water when equilibrium is reached, then the molecular concentration of the remaining acid and alcohol will be  $a-x$ , and that of the ester and water will be  $x$ . Hence, the above equation for the limit of the reaction becomes:—

$$k(a-x)^2 = k'x^2 \quad \text{or} \quad \frac{(a-x)^2}{x^2} = \frac{k'}{k}.$$

This ratio of  $k$  to  $k'$  is a constant independent of the concentration, and can be determined by an analysis of the reaction products when equilibrium has been attained; it is known as the *equilibrium constant*, and is represented by  $K$ . In the formation of esters it corresponds to the conversion of approximately two-thirds of the alcohol and of the acid into ester and water; if the original molecular concentrations of the alcohol and acid are 1, then, when equilibrium has been reached, their active masses will be  $1 - \frac{2}{3} = \frac{1}{3}$ , and that of the ester and of the water will be  $\frac{2}{3}$ . Inserting these figures in the equation, the value of the equilibrium constant for the reaction is obtained:—

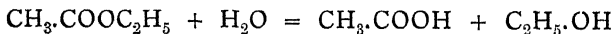
$$K = \frac{k'}{k} = \frac{\frac{1}{3} \times \frac{1}{3}}{\frac{2}{3} \times \frac{2}{3}} = \frac{1}{4}$$

This constant represents the ratio of the velocity constants of the two opposite reactions, and can, therefore, be made use of to determine the extent to which the esterification will proceed with any proportions of alcohol and acid. With three equivalents of alcohol to one of acid, 90 per cent. of the acid should be converted into the ester, and this figure is in accord with the experimental result; by still further increasing the proportion of alcohol, the esterifica-

tion of the acid can be made practically complete. Similarly, the complete esterification of an alcohol can be effected by sufficiently increasing the proportion of acid used.

For the practical preparation of ethereal salts, it is obviously necessary to adopt some means for preventing the reversal of the reaction between the alcohol and acid. This can be done by the addition of a suitable reagent to remove the water formed in the reaction; concentrated sulphuric acid or dry hydrochloric acid gas are usually employed, under conditions that will be described in Chapter XI.; occasionally, better results are obtained by the use of anhydrous salts as dehydrating agents. By this means both the acid and the alcohol can be completely converted into the ester. It was formerly regarded as necessary to employ a considerable quantity of the above acids to effect this dehydration, but it has since been shown<sup>1</sup> that from 2 to 3 per cent. of hydrochloric acid is quite sufficient to complete the esterification; the hydrochloric acid undergoes no change in the reaction, but simply accelerates it as a catalytic agent. Small quantities of sulphuric acid appear to act similarly.

*The Saponification of Ethereal Salts.*—The gradual decomposition of ethereal salts by water, into the acid and alcohol from which they have been formed, constitutes the reversal of the reaction for their preparation. When about one-third of the ethyl acetate, represented by the equation:—

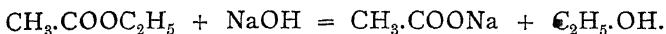


has been converted into acetic acid and ethyl alcohol, the four substances, ester, water, acid, and alcohol, are in equilibrium, as already stated, and the reaction is balanced. The decomposition proceeds farther if an excess of water be present, but only with extreme slowness, the extent of the decomposition being regulated by the active mass, in accordance with Guldberg and Waage's formula. The complete decomposition of the ester can, however, be readily effected by means of alkalis or of mineral acids;

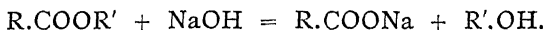
<sup>1</sup> E. Fischer and Speyer, *Berichte*, 1895, xxviii. 3201, 3252.

these decompositions are of both practical and theoretical importance.

The decomposition by alkalis, such as potassium or sodium hydroxide, is known as *Saponification*; it is the process employed in the manufacture of soap. When ethyl acetate is boiled with sodium hydroxide, ethyl alcohol is liberated, and sodium acetate is formed, according to the equation:—

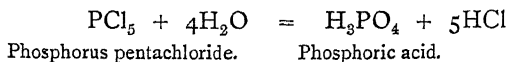


All esters are similarly decomposed, and the process of saponification can be represented by such a general equation as:—

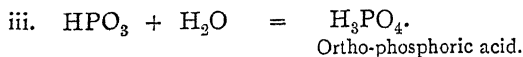
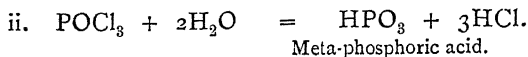
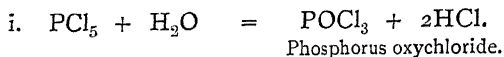


in which R and R' represent two radicals, either like or unlike.

Experimental investigations have shown that the rate of saponification of the simple esters is in accordance with that which would be expected from the law of mass action for an equation such as the above; it is a reaction between two molecules, a *bi-molecular reaction*. The velocity constant for the change is practically the same for equivalent solutions of the hydroxides of the alkali metals, and of the alkaline earths, calcium, strontium, and barium; but it varies with the nature of the alcohol or acid radical present in the ester, when one and the same base is employed in the saponification. The relation of this factor, the velocity constant, to the saponification of more complex esters, affords a valuable means for ascertaining the course of these more complicated decompositions. This constant depends upon the number of reacting molecules, and serves, therefore, for the determination of the latter. Reactions in which many molecules participate are commonly employed as representative of chemical changes. The action of water upon phosphorus pentachloride is, for instance, represented by the equation:—



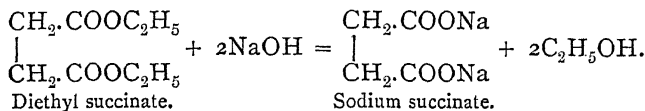
But this reaction can be followed through intermediate stages, which show that more than three molecules do not take part in the reaction at any one stage. These successive changes may be expressed by the equations:—



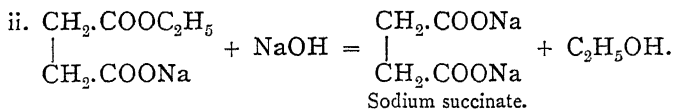
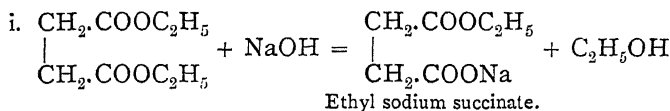
The first stage, involving the formation of phosphorus oxychloride, is bi-molecular, the second stage, in which meta-phosphoric acid is formed, is represented as ter-molecular, and the formation of ortho-phosphoric acid from the latter is again a bi-molecular reaction. The intermediate products represented in these equations are well known compounds, and thus the successive changes in the complete decomposition of phosphorus pentachloride by water are readily followed. But in many other reactions in which several molecules of the reacting substances are represented as taking part it is extremely difficult to obtain evidence of such intermediate stages by the ordinary chemical methods; it is, therefore, of great importance that the velocity constant affords a means for their recognition. The result of much experimental inquiry has been to show that almost all apparently complex reactions really proceed in stages, and comprise a series of successive simple reactions. These simple reactions are generally bi-molecular; ter-molecular changes are comparatively rare. The second decomposition represented above as the action of water on phosphorus oxychloride, for instance, is more probably the resultant of two bi-molecular reactions, and not a direct ter-molecular change.

The application of these considerations to the saponification of the esters of dibasic acids has been to prove that the decomposition proceeds in two stages. Thus, diethyl succinate, which is derived from succinic acid, just as ethyl acetate is derived from acetic acid, the esterification extending to each of the carboxyl groups present, when

completely saponified, forms sodium succinate and ethyl alcohol. The determination of the velocity constant of the reaction shows that the saponification does not proceed according to the single equation:—



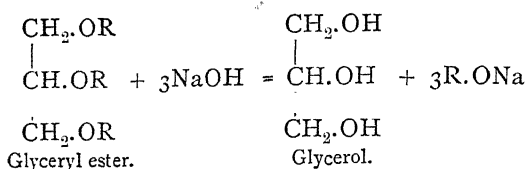
but in two successive stages, as follows:—



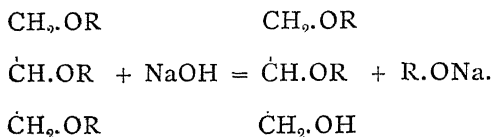
The first decomposition would be a ter-molecular reaction, the second, two successive bi-molecular reactions, involving two different velocity constants for the complete change. Guldberg and Waage's principle of mass action can thus decide between the two methods of decomposition, and the theoretical requirements of the latter change agree with the experimental data. That this view is correct is confirmed by heating the ester with only one-half of the alkali required for complete decomposition. According to the ter-molecular change, half of the ethyl succinate would be completely saponified and half left unchanged, but as a matter of fact 75 per cent. of the decomposition results in the formation of the ethyl sodium succinate, according to equation i.

The saponification of fats in the manufacture of soap is concerned with the decomposition of ethereal salts of the tervalent alcohol, glycerol. Each of the hydroxyl groups is in combination with an acid radical, the complete decomposition taking place according to the following general equation, in which R represents the acid radical:—





This decomposition appears as a quadri-molecular decomposition, but like other complicated reactions, it really proceeds in a series of successive bi-molecular changes, as has been proved by the experiments of Geitel<sup>1</sup> and of Lewkowitsch.<sup>2</sup> The initial change is accordingly represented by the equation:—



The acids that occur in combination with glycerol in fats are chiefly palmitic, stearic, and oleic acids. The two former, which have the formulæ  $\text{C}_{16}\text{H}_{32}\text{O}_2$  and  $\text{C}_{18}\text{H}_{36}\text{O}_2$  respectively, are higher acids of the acetic series, and their sodium salts, together with sodium oleate, are the essential constituents of ordinary soap.

The saponification of ethereal salts has several interesting laboratory applications. The method of ascertaining the number of hydroxyl groups present in an alcohol<sup>3</sup> is realised practically by converting it into an ethereal salt and saponifying the latter; the quantity of alkali required for the saponification is readily determined, and thus the number of acid groups that have combined with the original alcohol to form the ester is ascertained.

The velocity of saponification of esters has been used to determine the relative strengths of various bases, and the results obtained are in accord with those ascertained by other methods, such as the measurement of the electrical

<sup>1</sup> *J. Chem. Soc. Abstracts* 1900, lxxii. [ii.], 547.

<sup>2</sup> *Proc. Chem. Soc.*, vol. xv., 1900, No. 213, p. 190; and *Berichte*, 1900, xxxiii. p. 89; 1906, xxxix. p. 4095. Cf. also R. Wegscheider, *Monatsh. Chem.*, 1908, xxix., 83.

<sup>3</sup> Cf. Chap. viii. p. 144.

## ETHEREAL SALTS.

conductivity. Further, by comparing the velocity with which esters, such as methyl acetate, are saponified by aqueous solutions of the potassium salts of alcohols and of phenols, it has been possible to ascertain the relative extent to which such salts are hydrolysed in solution, since this velocity is dependent on the proportion of free alkali that results from their decomposition by water. The more acid character of phenol as compared with a saturated aliphatic alcohol (hexyl alcohol) is thus completely confirmed, the potassium salt of the latter being 90 per cent. hydrolysed, that of phenol<sup>1</sup> less than 7 per cent., under analogous conditions of experiment.

*The Hydrolysis of Ethereal Salts by Mineral Acids: Catalysis.*—The complete decomposition of ethereal salts by means of acids is a somewhat different process to their saponification by alkalis. The change is *catalytic*;<sup>2</sup> the acid acts as a catalyst and accelerates the decomposition, without itself undergoing any change. The products of the hydrolysis are acid and alcohol, as represented by the equation:—



and the change proceeds much more rapidly in dilute acid solution than in pure water.

One of the chief interests in this catalytic action lies in the fact that it has proved a valuable and reliable method for the determination of the relative strength of acids—*i.e.*, of measuring their relative chemical affinities. Since the decomposition proceeds gradually, it is possible to follow it accurately by analysing the products present at intervals during the reaction, and thus to compare the accelerating influence of different acids. The rate of change has been found to be proportional to the quantity of ethereal salt present; it is, therefore, in accord with the principle of mass action as stated by Guldberg and Waage. But since dilute solutions of acids are employed in the decomposition, the active mass of the water remains practically unchanged, and the reaction is accordingly uni-molecular, instead of being bi-molecular, as in the case of saponification. This brings it into line with the inversion of cane sugar and

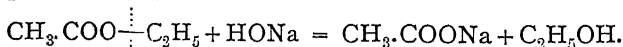
<sup>1</sup> Cf. Chap. viii. p. 147.

<sup>2</sup> Cf. Chapter vii. p. 117.

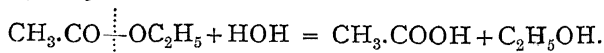
other decompositions which have been similarly employed for the determination of the affinity constants of acids. The methods have led to concordant results, which are also in agreement with the determination of the same constants by means of the electrical conductivity. The study of the catalytic hydrolysis of esters is also of interest, because it appears to be allied to some of the changes which are brought about by enzymes. These latter frequently show a catalytic action very analogous to that of inorganic substances.<sup>1</sup>

The catalysis of esters differs from their saponification, not only in being a uni-molecular change, but also in the manner in which the ethereal salt is attacked. This conclusion has been arrived at by comparing the velocity of the decomposition of esters containing different acid or alcohol radicals, by bases and acids. With esters containing the same acid radical but different alcohol radicals, the velocity of saponification by alkalis decreases with an increase in the molecular weight of the alkyl, but the difference in the velocity is far less marked when only the acid radical of the ester is changed. Exactly the reverse is the case when dilute mineral acids are employed for the decomposition. Since the hydroxyl group of bases and the hydrogen of acids are to be regarded as the initial agents in the change, the above experimental results lead to the conclusion that in the saponification by alkalis the ester molecule is attacked between the alcohol radical and the oxygen, in the catalysis by acids, between the acid radical and the oxygen, a difference that may be summarised by the following equations:—

*Saponification by Alkalis :—*



*Catalysis by Acids :—*



Although the study of the action of mass, reaction velocities, and affinity constants falls strictly within the

<sup>1</sup> Cf. Chap. vii, p. 117.

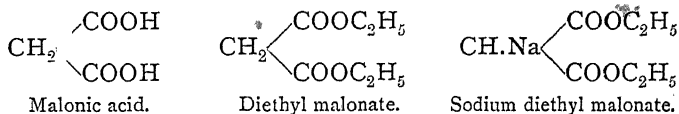
domain of physical chemistry, the applications of the results arrived at and their use in the proper interpretation of chemical change extend to every branch of the science. The above examples, which have been given in outline, will suffice to indicate the great value that is served by such applications, a value which is specially likely to develop an accurate knowledge of chemical reactions, carrying with it both important theoretical deductions and direct practical indications.

The fuller consideration of these subjects will be found in text-books on physical chemistry.<sup>1</sup>

*Some Synthetical Applications of Ethereal Salts.*—The ethereal salts serve as the starting point for very many syntheses of the most varied character. They are used for the preparation of ketones, acids, and ketonic acids, both aliphatic and cyclic, and there is hardly another class of compounds which has proved as prolific in its synthetical applications.

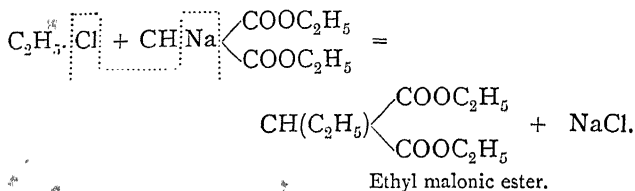
The most important and interesting of these reactions are dependent upon the power possessed by certain ethereal salts of forming derivatives in which an atom of hydrogen is replaced by sodium; these metallic derivatives react with a great variety of other compounds, and thus lead to the preparation of new substances. Many of the reactions involved also afford a valuable indication of the structure of the resulting products.

*Diethyl Malonate.*—In the diethyl ester of the dibasic acid, malonic acid, for instance, one of the two hydrogen atoms in the methylene group ( $\text{CH}_2$ ), may be replaced by sodium to form a compound, which may be provisionally regarded as having the following formula:—

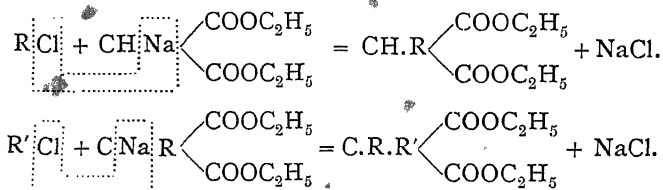


<sup>1</sup> *Introduction to Physical Chemistry*, J. Walker, fourth edition, 1907; *Theoretical Chemistry from the Standpoint of Arogradro's Rule and Thermodynamics*, Nernst, trans. by Leffeldt, 1904; *Lectures on Theoretical and Physical Chemistry*, van't Hoff, trans. by Leffeldt, 1898-1899; *Text-books of Physical Chemistry*, edited by Sir William Ramsay, 1904-8, a series of text-books dealing with the various branches of Physical Chemistry.

This sodium derivative reacts with many classes of halogen compounds, such as alkyl and acid chlorides, and the monohalogen substitution products of the esters of organic acids, such as ethyl monochloracetate  $\text{CH}_2\text{Cl}.\text{COOC}_2\text{H}_5$ , and thus gives rise to the esters of complex dibasic and polybasic acids. The reaction with ethyl chloride may be represented by the equation:—



The compounds of this type that are thus obtained from diethyl malonate are readily acted upon by sodium ethylate to form a compound in which the second hydrogen atom of the original methylene group is replaced by the metal. This new sodium derivative reacts similarly to the initial sodium compound; thus, a great variety of substances can be obtained, especially when it is remembered that different radicals can be substituted for each of the sodium atoms successively introduced. Representing the group in combination with the halogen element by R or R', which may be like or unlike, the following general equations will express these reactions:—

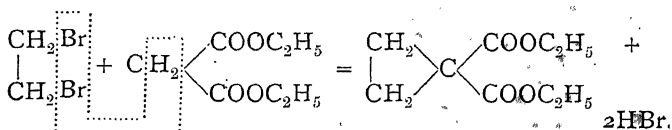


By the saponification of such ethereal salts the corresponding dibasic or tribasic acids are obtained, and these, like all polybasic acids containing two or more carboxyl groups attached to one and the same carbon atom,<sup>1</sup> readily

<sup>1</sup> Cf. Chapter viii., p. 157.

lose carbon dioxide on heating; the malonic ester synthesis is thus extended to the preparation of monobasic acids.

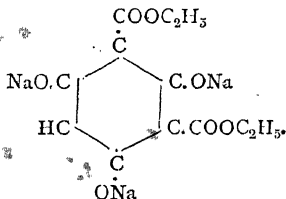
Saturated cyclic compounds, such as trimethylene derivatives, are obtained from sodium diethyl malonate by the action of the dihalogen derivatives of the hydrocarbons, such as ethylene dibromide, a change that can be most simply represented thus:—



Trimethylene dicarboxylic ester.

This reaction, which can be extended to homologues of ethylene dibromide and allied substances, has been the most important means of preparing the polymethylene compounds.

The synthesis of a benzenoid compound is effected by heating the sodium derivative of the ester with the ester itself. The reaction is a complex one, and it is probable that the initial product of the change undergoes a subsequent decomposition, previous to the formation of the substance finally obtained, viz.:—the sodium salt of the dicarboxylic ester of a tri-hydroxybenzene, phloroglucinol,<sup>1</sup> a compound having the formula:—

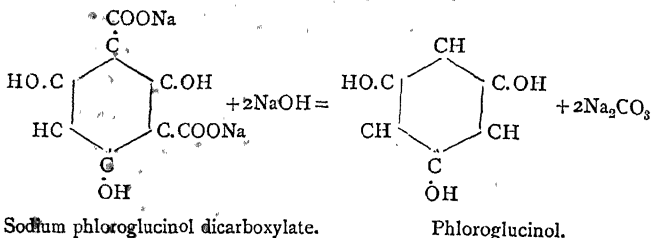


Ethyl phloroglucinol dicarboxylate.

<sup>1</sup> Cf. Moore, *J. Chem. Soc.*, 1904, lxxxv. 165.

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The ester yields the free dicarboxylic acid on saponification, and the latter, when fused with alkali, loses carbon dioxide to form trihydroxybenzene, just as benzoic acid is decomposed to form benzene:—



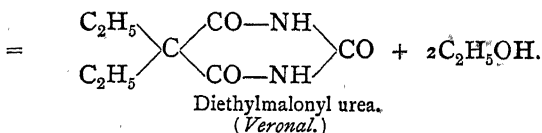
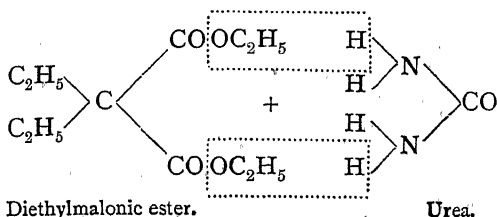
This and allied reactions in which cyclic compounds are obtained from aliphatic substances were formerly regarded as having an important bearing on the structure of benzene and its derivatives, but more detailed studies have shown that their value in this respect is fallacious. The initial compounds used for these syntheses have generally a two-fold chemical character, and in their reactions they may function in different ways, behaving indeed as if they had two different formulæ, according to the nature of the products with which they react or the conditions of the reactions. Hence, the results are inconclusive, a fact that is further complicated by the possibility that the compounds synthetically formed may also be capable of exerting a two-fold chemical character, as is actually the case with phloroglucinol.<sup>1</sup>

The valuable hypnotic veronal<sup>2</sup> furnishes a further example of the formation of a cyclic compound from diethyl malonate. By the successive replacement of the two hydrogen atoms of the  $\text{CH}_2$  group by sodium and by the ethyl radical, as explained above, diethylmalonic ester is obtained; by heating this ester with urea the alkyl-ester groups are eliminated with the formation of a closed-chain containing two atoms of nitrogen, which is known as the malonyl-urea or pyrimidine ring:—

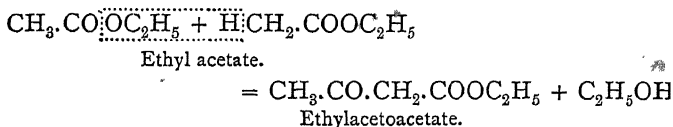
<sup>1</sup> Cf. Chapter xiv., p. 398.

<sup>2</sup> Cf. Chapter xvi., p. 468.

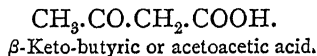
# ETHEREAL SALTS.



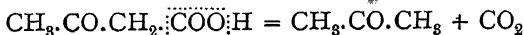
*Ethylacetoacetate*. — This compound — discovered by Geuther in 1863 — is obtained by the action of metallic sodium on ethyl acetate, and is the starting point for the synthetical preparation of many groups of compounds by means of reactions analogous to those detailed with diethyl malonate. It results from the combination of two molecules of ethyl acetate with the elimination of a molecule of ethyl alcohol, a change that may be provisionally represented by the equation :—



The function of the sodium, which is not represented in this equation, will be subsequently discussed. Ethylacetoacetate is the ethyl ester of a ketonic acid:—



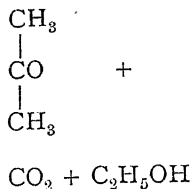
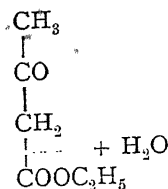
and as such behaves both as a ketone and as an ethereal salt. It is very easily saponified by treatment with dilute alkali, even at the ordinary temperature, but the resulting free acid is extremely unstable and decomposes most readily into acetone and carbon dioxide :—



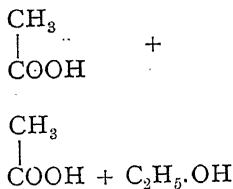
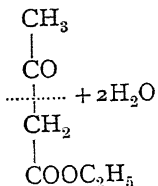


Ethylacetoacetate is markedly more stable than the free acid, the ethyl group giving a similar increased stability to the molecule to that observed in the case of many di- and tri-hydroxy-compounds;<sup>1</sup> but under the influence of both alkalis and dilute mineral acids it undergoes two forms of decomposition, which are the key to many of the important synthetical applications of the ester. These decompositions are known as the *ketonic* and *acid decompositions* respectively, from the nature of the resulting compounds:—

I. Ketonic decomposition.



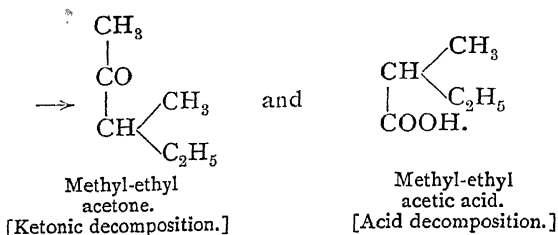
II. Acid decomposition.



The break occurs at different parts of the chain in the two reactions, as indicated by the dotted lines, resulting in the formation of acetone, carbon dioxide and alcohol in the first case, and of two molecules of acetic acid and one of alcohol in the second. The latter decomposition is favoured by concentrated solutions of alkali, the former by dilute solutions of alkali and by acids; but the two changes usually take place side by side, to a varying extent, with the derivatives of ethylacetoacetate, so that it is seldom possible to restrict the change to one decomposition.

<sup>1</sup> Cf. Chap. viii., p. 127.





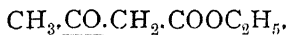
The great value of these syntheses lies rather in the simplicity and reliability of the method as a proof of the structure of the products obtained than in the vast number of compounds that can be thus prepared, although some of these have proved of service in the study of other groups.

In the synthesis of cyclic compounds ethylacetoacetate has proved of the greatest utility; it is one of the materials employed in the preparation of antipyrine,<sup>1</sup> and is made in large quantity for the manufacture of this valuable febrifuge, whilst amongst other applications, it has served as the starting point in one of the earlier syntheses of uric acid.

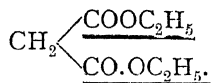
*The Structure of the Sodium Derivatives of Ethylacetoacetate and of Diethyl malonate.*—The provisional formulæ for the sodium derivatives of ethylacetoacetate and of diethyl malonate used above in representing the characteristic reactions of these compounds were formerly regarded as satisfactory. Although it was recognised that the hydrogen atoms of a  $\text{CH}_2$  group are not normally replaceable by metals—for instance, in the hydrocarbons or in the homologues of ethyl alcohol—the presence of certain acidifying or electro-negative groups was regarded as capable of conferring this property on the hydrogen atoms of the adjacent methylene group. In diethyl malonate the two carboxy-ethyl groups were looked upon as exerting this function; in ethylacetoacetate it was attributed to the joint influence of a ketonic and of a carboxy-ethyl group. These acidifying groups are underlined in the following formulæ:—

<sup>1</sup> Cf. Chap. xv., p. 407.

# ETHEREAL, SALTS.



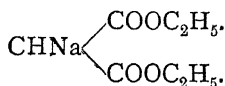
Ethylacetoacetate.



Diethyl malonate.



Sodium ethylacetoacetate.

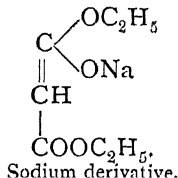
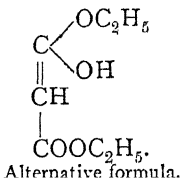
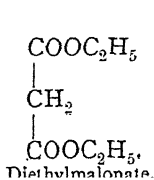
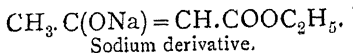
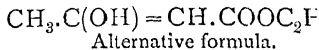
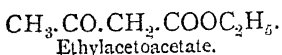


Sodium diethyl malonate.

Similar acidifying groups are present in many other compounds which share with the above this characteristic of containing similarly replaceable hydrogen atoms. There is no doubt that specific substituting groups have a marked influence on the chemical behaviour of compounds, and, therefore, this interpretation of the salt-forming power of these esters appeared quite admissible. It had, moreover, the quality of representing the chief reactions of these sodium compounds in a simple and direct manner. But a general study of the sodium derivatives of organic compounds has shown that this acidifying influence is, with a few exceptions, restricted to radicals containing oxygen. Methylene chloride,  $\text{CH}_2\text{Cl}_2$ , for instance, does not yield sodium derivatives, despite the presence of the two atoms of chlorine, a strongly electro-negative element. The only case in which there is good reason for assuming a direct linking of a metal to carbon in organic compounds is in the metallic derivatives of acetylene.<sup>1</sup> The outcome of a critical study of very many groups of compounds which form these sodium and other metallic derivatives has been the conclusion that the metal is linked to an oxygen atom of the molecule and not to carbon, as represented in the above formulæ. That a hydrogen atom in combination with oxygen is readily replaceable by metals, especially sodium, in organic compounds, is amply illustrated in such substances as the acids, alcohols and phenols, and whenever a similar condition of replacement is possible in other compounds it is now regarded as the more probable course of the substitution. This similarity is not possible with the structural formulæ for ethylacetoacetate and diethyl malonate hitherto employed, but by representing

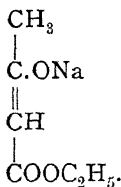
<sup>1</sup> Cf. Chap. iv., p. 48.

these compounds by an alternative formula, both may be shown to contain an hydroxy-group, from which sodium salts may be derived. on normal lines:—

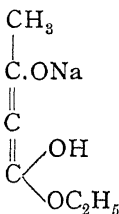


The relation of the two structural formulæ for these compounds will be discussed in Chapter XIV.; meanwhile, it will suffice to note that the formation of the hydroxyl group arises, in both cases, by the change in position of one of the methylene hydrogen atoms, accompanied by the formation of a double bond between two of the carbon atoms.

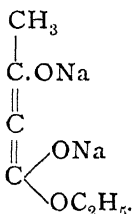
By a repetition of this molecular arrangement di-sodium salts might be possible, in both cases, on the following lines:—



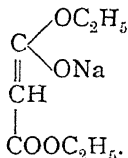
Sodium ethylacetoacetate.



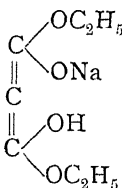
Alternative formula.



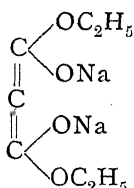
Di-sodium derivative.



Sodium diethyl malonate.

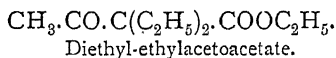
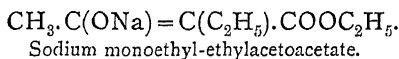
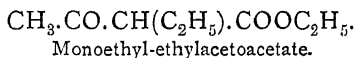
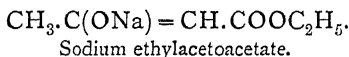


Alternative formula.



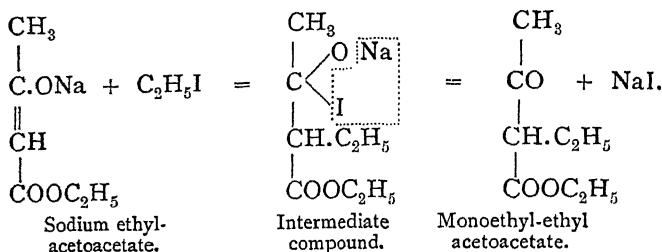
Di-sodium derivative.

There is, however, no satisfactory evidence that such salts can be obtained, and this is quite in accord with the generality that the acid character of a compound is decreased by the introduction of a metal. This is observed, for instance, in the case of phosphoric acid,  $\text{H}_3\text{PO}_4$ ; there is a marked diminution in the heat evolved by the successive replacement of the three hydrogen atoms by sodium to form the salts  $\text{NaH}_2\text{PO}_4$ ,  $\text{Na}_2\text{HPO}_4$ , and  $\text{Na}_3\text{PO}_4$ . When the sodium atom in the above esters is replaced by an alkyl or other radical, this influence is, of course, removed, and the second hydrogen atom can then be replaced by the metal, as already stated. Making use of the hydroxylic formulæ for the sodium salts, the products of the successive action of sodium and ethyl iodide upon ethylacetoacetate will have the following formulæ:—



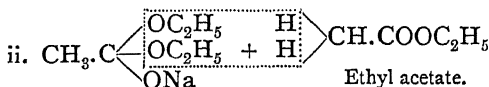
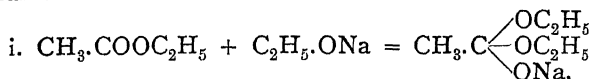
There is full proof that the formulæ of these alkyl derivatives of the ester are correct, and that the ethyl groups, in both the mono- and di-ethyl compounds, are attached to the carbon atom of the original methylene radical, and this is also the case with the analogous derivatives of diethyl malonate. This structure was obvious from the equations given earlier in this chapter, in which the sodium was represented as replacing a hydrogen of the methylene group, but it requires explanation in respect to the acceptance of the hydroxylic formula for these sodium salts, since direct substitution would lead to compounds in which the alkyl group is attached to oxygen instead of to carbon. This apparently abnormal behaviour can be accounted for by the assumption that the sodium compound, since it contains an ethylene or unsaturated linking, first adds a molecule of ethyl iodide to form a saturated,

intermediate compound, which subsequently separates sodium iodide. These changes are shown in the following equations. It will be noted that the separation of the sodium iodide occurs with the substituents attached to one and the same carbon atom, whereas the constituents of the previously-added molecule of ethyl iodide are linked to adjacent carbon atoms:—



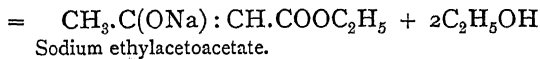
The formation of such intermediate compounds as the above allows of a very plausible interpretation of many analogous changes; the compounds themselves are, as a rule, too unstable to be isolated, but direct proof of their formation has been obtained in several instances. In their bearing on the synthesis of ethylacetoacetate itself they afford a good explanation of the part played by the sodium in this reaction. In the simple equation employed above for representing the formation of the ester from two molecules of ethyl acetate, the function of the sodium in the reaction is not indicated. It was found by Ladenburg (1870) that the reaction does not take place at the ordinary temperature if due care be taken to remove the last traces of ethyl alcohol from the ethyl acetate employed. As ordinarily prepared, this ester always contains a little ethyl alcohol, and the formation of the acetoacetate is really due to its presence. It is the ethyl alcohol, and not the ethyl acetate, that is first attacked by the sodium, forming sodium ethylate,  $\text{C}_2\text{H}_5\text{ONa}$ , with liberation of hydrogen; this then acts upon the ethyl acetate to produce an intermediate compound, which, in presence of a second molecule of ethyl acetate, forms the sodium derivative of the acetoacetate with the regeneration of a molecule of alcohol, in addition to that separated in the reaction. The liberated

alcohol is then further acted upon by the sodium, and in this way the cycle of changes is repeated; the action is fermentative in character, since a trace of ethyl alcohol is all that is necessary to start the formation of the acetoacetate, further proportions of alcohol being formed continuously, as the reaction proceeds. This view of the mechanism of the change, which is represented by the following equations, is due to Claisen and Lowmann (1887); it is confirmed by the observation that the reaction may be brought about by sodium ethylate without the addition of any metallic sodium:—



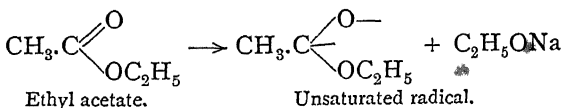
Ethyl acetate.

Intermediate compound.



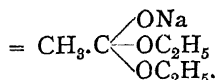
Sodium ethylacetoacetate.

The sodium derivative then yields the free ethylacetoacetate on treatment with dilute acetic acid. It will be noted that the formula for the sodium salt, indicated by this course of the reaction, conforms with that accepted from other considerations. The formation of such an addition product as the above from a saturated molecule like ethyl acetate is due to a rearrangement of the atomic affinities, similar to that observed in the case of ketones and aldehydes,<sup>1</sup> thus allowing it to function as an unsaturated radical:—



Ethyl acetate.

Unsaturated radical.



Intermediate compound.

<sup>1</sup> Chap. viii., p. 127.



Beyond the theoretical interest that attaches to the study of the structure of the sodium salts of diethyl malonate and of ethylacetoacetate, and further to the mechanism of the reaction employed for the preparation of the latter, these views have received confirmation from the very numerous extensions of the reaction to the preparation of allied substances.

## CHAPTER X.

### DERIVATIVES OF THE HYDROCARBONS CONTAINING NITROGEN.

Nitrogen an important constituent of products of animal and vegetable origin—Synthetical and technical importance of derivatives of the hydrocarbons containing Nitrogen.

*Compounds containing Nitrogen linked to Carbon alone:—*Cyanogen, Hydrocyanic acid and its alkyl derivatives.

*Compounds containing Nitrogen linked to Oxygen:—*Nitro-compounds and Nitrates; their structure and explosive properties.

*Compounds containing Nitrogen linked to Hydrogen:—*The Amines and their derivatives—Amides—The basicity of organic compounds—Derivatives of Hydrazine and of Hydrazoic acid.

*Compounds containing Nitrogen linked to Nitrogen:—*Diazo- and Azo-compounds. The structure of Diazo-compounds.

*Empirical laws of Substitution in benzenoid compounds.*

*Uric acid and allied compounds:—*Urea. Hippuric acid. Uric acid.

*The Polypeptides.*

THE importance of nitrogen as a constituent of compounds of animal origin was recognised by Lavoisier. Together with carbon, hydrogen, and oxygen, and occasionally phosphorus and sulphur, it is a characteristic constituent of the products of animal metabolism, the substances which result from the breaking up of proteins, by means of chemical or bacterial agencies.

The proteins, of which ordinary egg-albumin is a familiar example, form the most important part of the cell-contents of both animals and plants. They are highly complex compounds, consisting of carbon, hydrogen, oxygen, and nitrogen, and in most cases of sulphur and phosphorus in addition; but, beyond certain details concerning their physical properties and behaviour towards reagents, comparatively little is as yet known of their chemical nature, though great advances have been made in this direction during the past few years. Their in-

vestigation is rendered exceptionally difficult by the fact that, with a few exceptions, they cannot be obtained crystalline or be distilled without decomposition; they are colloidal substances, and are further characterised by a great tendency to form unstable compounds with other substances which occur side by side with them in the tissues of plants and animals, and from which it is difficult to isolate them in a state of purity. As a consequence, no means are at present known for establishing satisfactory criteria of their chemical individuality. By the action of acids, alkalis, enzymes, and putrefactive bacteria the proteins are broken down into simpler molecules, which retain many of the empirical characteristics of the original substances. The study of these decomposition products has disproved the former view that albumin is a substance of definite composition and properties, and has shown that there are many forms of albumin which differ in their properties, complexity, and chemical character. Amongst the products that result by the action of the above reagents are a variety of complex amino-acids, and an important advance has recently been made towards a more accurate knowledge of the proteins by the synthetical preparation of several allied amino-compounds.<sup>1</sup> Their more ultimate decomposition products, such as urea, uric acid, and hippuric acid, the excretory products of carnivora and herbivora, have been long known as stable, crystalline compounds; it has consequently been possible to isolate them in a state of purity, and, moreover, to ascertain their structure and to effect their synthesis.

Turning to synthetical organic chemistry, the derivatives of the hydrocarbons containing nitrogen include substances of the greatest technical importance and theoretical interest. The preparation of nitrobenzene by Mitscherlich in 1834, followed by its reduction to aniline by Zinin in 1842, supplied the initial reactions on which the aniline colour industry is based; in addition, many valuable drugs, such as phenacetine and antifebrine, and explosives, such as picric acid, are included amongst the nitrogen-containing derivatives of the aromatic hydrocarbons. Amongst aliphatic compounds, the alkyl derivatives of ammonia, discovered by Würtz in 1848, and systematised by the

<sup>1</sup> Cf. this Chapter p. 226.

## COMPOUNDS CONTAINING NITROGEN.

classical investigations of A. W. Hofmann<sup>7</sup>, (1850), have recently led to important developments in stereochemistry, whilst the subjects of dynamic isomerism, molecular rearrangement, and empirical laws of substitution amongst benzenoid compounds, have received important, and in some cases their chief developments from the study of nitrogenous compounds. The diazo-compounds in particular have formed the subject of the most prolonged and careful investigation, and the researches on their constitution form one of the most interesting chapters of modern chemistry.

The scope of the present chapter will be restricted to a general consideration of nitrogen compounds as typified by comparatively simple derivatives of the hydrocarbons; in addition, certain compounds will be described, of which the stereochemical or other isomeric relations will be discussed subsequently. Some details in respect to recent investigations on uric acid and related substances of animal and vegetable origin, and on the synthetically prepared protein-like substances called "polypeptides," will conclude the study of this group of compounds.

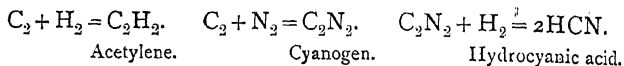
In order to systematise this review of the nitrogen-containing derivatives of the hydrocarbons, they may be conveniently grouped, according to the condition of linking of the contained nitrogen, on the following lines:—

- I. *Compounds containing Nitrogen linked to Carbon alone*—Cyanogen. Hydrocyanic acid and its alkyl derivatives.
- II. *Compounds containing Nitrogen linked to Oxygen*—Nitro-compounds and Nitrates.
- III. *Compounds containing Nitrogen linked to Hydrogen*—The amines and their derivatives. Amides. Derivatives of hydrazine and of hydrazoic acid.
- IV. *Compounds containing Nitrogen linked to Nitrogen*.—Diazo- and Azo-compounds.
- V. *Uric acid and allied compounds. The Polypeptides.*

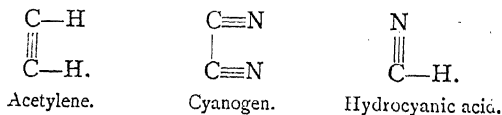
I. *Compounds containing Nitrogen linked to Carbon alone. Cyanogen. Hydrocyanic acid and its Alkyl derivatives.*—Cyanogen and hydrocyanic acid, which constitute the simplest of these compounds, form, from a structural standpoint, the basis of the metallic cyanides and of the

complex cyanogen compounds, such as the ferro- and ferricyanides, and Prussian blue, which are generally included in the inorganic division of chemistry. The simpler cyanogen compounds, however, especially as the source of well-defined alkyl derivatives, are more accurately classed as organic compounds.

Cyanogen itself is formed when an electric arc is completed between carbon electrodes in an atmosphere of nitrogen, whilst cyanogen and hydrogen combine to form hydrocyanic acid under the influence of the silent electrical discharge. This direct combination of the elements is analogous to that of carbon and hydrogen to form acetylene:—



Structurally these compounds can also be compared, hydrocyanic acid being regarded as derived from acetylene by the replacement of the tervalent methine group CH, by an atom of nitrogen:—



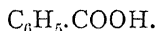
The univalent radical, CN, is evident in these two cyanogen compounds; its importance in the development of the radical theory has already been referred to.<sup>1</sup> It possesses a remarkable power of uniting with itself to form polymeric compounds, a property that is also seen amongst the complex inorganic cyanides. The cyanogen radical has a marked acidifying influence, analogous to that of chlorine. Thus cyanoacetic acid, cyanobenzoic acid, and cyanophenol are much stronger acids than acetic acid, benzoic acid, and phenol respectively, and even cyanoform,  $\text{CH}(\text{CN})_3$ , is a moderately strong acid. Further, whilst diethyl malonate is scarcely sufficiently acidic to form alkali salts, the corresponding compound, in which a hydrogen atom is replaced by the cyanogen radical, can decompose carbonates. In combination with hydroxyl the cyanogen

<sup>1</sup> Chapter ii., pp. 16 and 19.

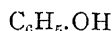
group forms cyanic acid, an acid of moderate strength; with hydrogen it forms hydrocyanic or prussic acid, but the latter is an extremely weak acid, a fact related to its structural formula, as will be pointed out subsequently.



Acetic acid.



Benzoic acid.



Phenol.



Cyanoacetic acid.



Cyanobenzoic acid.



Cyanophenol.



Diethyl malonate.



Diethyl cyanomalonate.

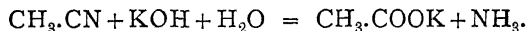
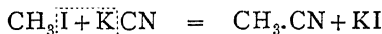


Cyanic acid.



Hydrocyanic acid.

*The Alkyl Derivatives of Hydrocyanic Acid.*—The replacement of the hydrogen of hydrocyanic acid by an alkyl radical cannot be effected directly, but certain salts of the acid react readily with methyl iodide and its homologues. The resulting products are different, however, according to the salts used in their preparation. On heating methyl iodide and potassium cyanide, for instance, the product of the reaction contains the alkyl group directly attached to the carbon of the cyanogen group. This is proved by the action of acids or alkalis which give rise to organic acids, compounds in which the alkyl group is, beyond a doubt, attached to the carbon of the carboxyl; the nitrogen of the cyanogen group is converted to ammonia. The formation of the cyanide and its decomposition take place according to the equations:—



Methyl cyanide or acetonitrile.

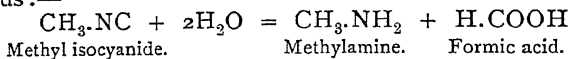
Potassium acetate.

The latter decomposition forms an important synthetical method for the preparation of acids.<sup>1</sup>

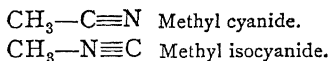
If silver cyanide be used instead of potassium cyanide in the preparation, a product is obtained which differs from the above-mentioned methyl cyanide in all its properties. Whereas methyl cyanide boils at 81°, possesses a fairly pleasant smell and a toxic action similar to that of

<sup>1</sup> Cf. Chapter viii., pp. 132 and 138.

hydrocyanic acid, the compound obtained from silver cyanide, which is called an isocyanide, boils at  $58^{\circ}$ , has a most obnoxious smell, and although also poisonous, differs widely from its isomer in its physiological properties. These physical and physiological differences are associated with a marked difference in chemical behaviour, which proves that the alkyl is attached to the nitrogen of the cyanogen group, and not to the carbon. Amongst the many reactions which substantiate this conclusion, that with dilute mineral acids may be cited, which yield formic acid and methylamine thus:—

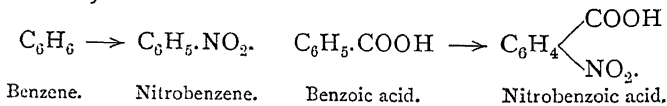


Comparing the structure of these two alkyl derivatives of hydrocyanic acid:—



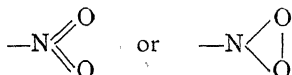
it is obvious that either potassium and silver cyanide must be structurally different, or that some molecular rearrangement must occur in the above reactions. This point, together with the relation of the alkyl compounds to hydrocyanic acid itself, will be discussed under dynamic isomerism. (Chapter XIV.)

II. *Compounds containing Nitrogen linked to Oxygen. Nitro-compounds and Nitrates; their Structure and Explosive Properties.*—The very marked difference in the behaviour of aliphatic and aromatic hydrocarbons towards nitric acid is a most valuable means for differentiating the two groups.<sup>1</sup> Whereas the former are usually very stable towards this reagent, the latter are readily attacked with the formation of the important derivatives known as the *nitro-compounds*. Nitrobenzene, for instance, is thus derived from benzene, and practically all derivatives of the benzenoid hydrocarbons containing the most varied substituting groups can be similarly nitrated.

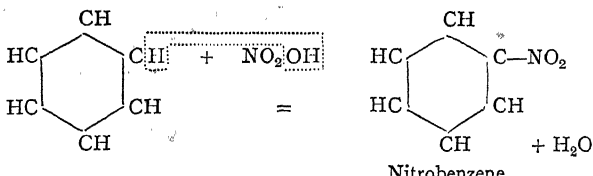


<sup>1</sup> Cf. Chap. v., p. 65.

The nitro-group, the radical which is introduced by the action of nitric acid, contains the nitrogen directly combined with oxygen, either as,

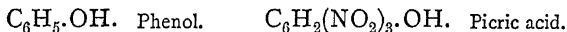


In the formation of nitrobenzene it replaces a hydrogen atom in the benzene ring, its introduction being accompanied by the separation of water, according to the equation:—



The ease with which this nitration occurs, added to the fact that the aromatic hydrocarbons are the most accessible compounds of the group, has rendered this reaction of great value in the synthetical preparation of benzenoid compounds.

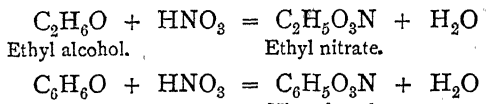
As an acid radical the nitro-group carries its electro-negative or acid character into all its derivatives; picric acid, for instance, the trinitro-derivative of phenol, is one of the strongest organic acids, whereas phenol itself is so weak that its salts are decomposed by carbonic acid gas.



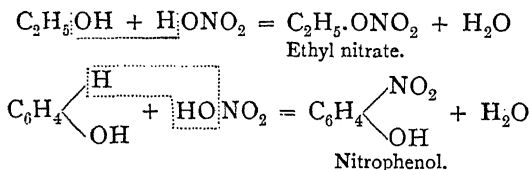
Mono- and di-nitrophenols are intermediate in acidity between these two compounds. The formation of a nitro-compound by the direct action of nitric acid upon phenol stands in marked contrast to the reaction between the aliphatic alcohols and nitric acid. Ethyl alcohol yields an ethereal salt, ethyl nitrate, and the polyvalent alcohols, such as glycerol and cellulose, the so-called "nitro-glycerine" and "nitro-cellulose," which are also nitric esters; the latter have but one common property with picric acid—that of explosibility. These two classes of compounds, nitro-compounds and nitrates, differ in respect



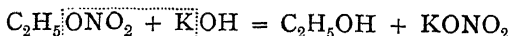
to the manner in which the contained nitro-group is linked in the molecule. The reactions employed to establish this fact are again typical, as in the case of the alkyl derivatives of hydrocyanic acid, of the methods adopted to differentiate the structure of compounds. Taking ethyl nitrate and nitrophenol as illustrations, their formation takes place according to the equations:—



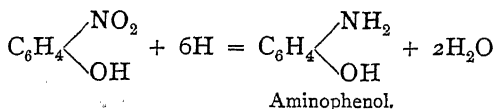
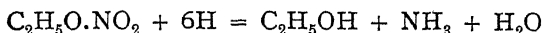
It is seen that in both cases the nitric acid replaces a hydrogen atom of the original compound by the group  $\text{NO}_2$ , but the manner in which this group is attached to the remainder of the molecule is not indicated. The reactions of ethyl nitrate show that it is a true ester, since it is saponified by alkalis; the nitro-group is therefore linked to oxygen. Nitrophenol, on the other hand, forms salts with alkalis, but does not undergo decomposition. On reduction it yields aminophenol, proving that the hydroxyl of the phenol molecule remains intact in the nitro-derivative and that the nitro-group is linked to a carbon atom of the ring, whilst ethyl nitrate gives ethyl alcohol and ammonia. The separation of water must, therefore, take place differently in the two preparations; in the formation of ethyl nitrate the hydroxyl group of the alcohol and the hydrogen of the nitric acid are separated, whilst in the case of nitrophenol it is a hydrogen atom of the ring that is eliminated. These changes are more fully expressed by the following equations:—



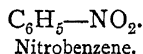
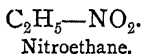
In the saponification of ethyl nitrate the primary reaction takes place according to the equation:—



The reaction is complicated by a simultaneous oxidation of the alcohol, which takes place at the expense of the potassium nitrate; the products which are actually isolated are, therefore, oxidation products of the alcohol. There is, however, no doubt that the first stage of the reaction takes place as represented above. The reduction of ethyl nitrate and of nitrophenol is represented by the following equations:—



This difference in the point of attack by the nitric acid, which is obviously consistent with the general stability of aliphatic hydrocarbons towards this reagent, also indicates that, in order to obtain true nitro-compounds in the aliphatic group, indirect methods must preferably be employed, although recent researches have shown that under suitable conditions many of the aliphatic hydrocarbons can be directly nitrated. The methods for the preparation of the aliphatic nitro-compounds were only realised long after the aromatic nitro-compounds were known, nitromethane and its homologues being first independently prepared by Victor Meyer and H. Kolbe in 1872; structurally, they are exactly analogous to the aromatic nitro-compounds, the nitro-group being directly attached to the alkyl radical:—



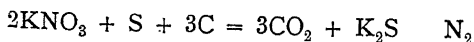
“Nitroglycerine” and “Nitrocellulose” were originally believed to be true nitro-compounds; they are, however, saponified by alkalis, but the resulting glycerol and cellulose are simultaneously oxidised as in the case of ethyl nitrate. Their general behaviour shows that they are esters of nitric acid, not nitro-compounds; their ordinary names are consequently misnomers, nitro-glycerine being really glycerol trinitrate, and nitrocellulose a mixture of different nitrates of cellulose.

The explosive nature of these esters and of picric acid is

to be attributed in part to a state of internal strain in the molecule, and in part to the presence, side by side, of oxygen and of elements (carbon and hydrogen) which can combine with oxygen with evolution of great heat. The state of strain of the nitro-group is evidenced by the relatively small heat of formation of highly nitrated compounds as compared with that of the non-nitrated substances. This is shown in the following instances:—

	<i>Heat of formation per gram, in calories.</i>		<i>Heat of formation per gram, in calories.</i>
Ethyl alcohol	1520	Mononitrobenzene (solid)	64
Ethyl nitrate	333	<i>m</i> -Dinitrobenzene . . .	40
			26
Glycerol . . .	1758	Phenol . . .	391
Nitroglycerine . . .	406	Trinitrophenol	204

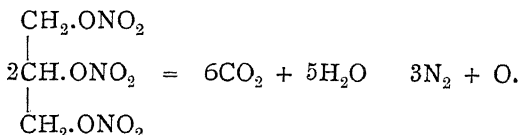
In some cases—as, for instance, that of nitrogen iodide or silver acetylide—the internal strain is in itself sufficient to render the compound highly explosive, but in the nitro-compounds the main determining factor is the presence in the molecule of elements which are capable of forming new and more stable molecules.<sup>1</sup> The conditions favourable to explosion may be either extraneous to the explosive molecule or self-contained. Ordinary black gunpowder, for example, contains the nitro-group in the form of potassium nitrate, which is admixed with carbon and sulphur; when fired, carbon dioxide, potassium sulphide, and free nitrogen are formed as the essential products of the decomposition, although, owing to incomplete mixture, other reactions occur locally:—



This change is accompanied by a large evolution of gas and also of heat; hence, a sudden increase of pressure, the characteristic of an explosive, is the result. The extraneous conditions necessary for explosion, as realised in the case of gunpowder by mechanical admixture, are supplied in the explosive nitrates and picric acid in the far

<sup>1</sup> The atomic groupings which bring about an intra-molecular strain are discussed in van't Hoff's *Lectures on Theoretical and Practical Chemistry*, translated by Leffeldt (1903), Part iii. p. 103.

more intimate condition of chemical combination. Dynamite, for instance, which consists of glycerol nitrate held in suspension in very porous sand, so as to give safety in handling, can decompose, when fired, according to the equation:—



Glycerol trinitrate (Nitroglycerine).

In practice it is found that the ratio of the products of explosion varies somewhat according to the pressure of the gases. The oxygen present in nitroglycerine is just in excess of that required to combine with the total carbon and hydrogen present; the formation of both water and carbon dioxide is attended with a large evolution of heat, and the products of combustion are entirely gaseous. Conditions similarly favourable to explosibility are present in gun-cotton, a mixture of cellulose nitrates, and in blasting gelatine, which is a colloidal mixture of gun-cotton with nitroglycerine. The oxygen contained in picric acid is considerably less than is necessary for the complete combustion of the carbon and hydrogen present, and the carbon is therefore converted principally to carbon monoxide; picric acid has nevertheless powerful explosive properties when fired under suitable conditions, and has found extensive use in the form of lyddite, melinite, and the Japanese explosive, shimose.

The presence of the nitro-group, which is thus an important factor in conferring explosive properties on the above compounds, contributes also, by virtue of its electro-negative character, to the instability of the compounds into which it is introduced. Thus, the chlorine is much more readily displaced from chlornitrobenzene than from chlorbenzene. A practical method is thus provided for isolating certain parent substances from their derivatives. For instance, whereas phenyl azoimide (page 204) is quite stable towards alkalis, its nitro-derivatives can be decomposed by this reagent with the formation of the free

azoimide or hydrazoic acid,<sup>1</sup>  $N_3H$ , a compound which was first prepared by Curtius (1890) from its organic derivatives.

III. *Compounds containing Nitrogen linked to Hydrogen. The Amines and their Derivatives. Amides. The Basicity of Organic Compounds. Derivatives of Hydrazine and of Hydrazoic Acid.*—By the replacement of one or more hydrogen atoms in ammonia by an organic radical a series of compounds called *amines* is derived, which share the basic character of ammonia to a greater or less extent, according to the nature of the organic radical they contain. The aliphatic amines, such as methylamine and its homologues, are somewhat stronger bases than ammonia, whilst aniline, the typical representative of the aromatic amines, is a much weaker base, owing to the acidifying influence of the phenyl group, an influence already noticed in connection with the stability of the salts of phenol.<sup>2</sup> Diphenylamine, which contains two phenyl groups, is a very much weaker base than aniline for the same reason, whilst triphenylamine has no basic properties.

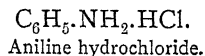
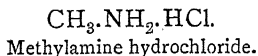
$NH_3$	$CH_3NH_2$	$C_6H_5NH_2$	$(C_6H_5)_2NH$	$(C_6H_5)_3N$
Ammonia.	Methylamine.	Aniline.	Diphenylamine.	Triphenylamine.

The amines containing only one organic radical are termed primary amines. In these the nitrogen is united to two hydrogen atoms, the third affinity of the tervalent element being directly attached to carbon. This is fully proved by the methods of formation and by the decompositions of the amines. The group,  $NH_2$ , which is thus attached to the organic radicals is known as the *amino-* or *amido-group*. The basic influence of this group is shown in the power possessed by these amines of forming salts with acids. Just as ammonia forms ammonium chloride by direct combination with hydrochloric acid, so methylamine and aniline combine directly with this acid to form well-defined salts:—

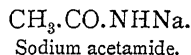
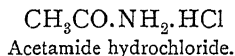
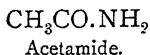
$NH_4Cl$	$CH_3.NH_3Cl$	$C_6H_5.NH_3Cl$
Ammonium chloride.	Methylammonium chloride.	Phenylammonium chloride.

<sup>1</sup> Grandmougin and Noelting, *Berichte*, 1892, xxv. 3342.  
<sup>2</sup> Cf. Chap. viii., p. 154.

The latter are more generally written as follows, but the analogy with, and structural relation to, ammonium chloride are best shown by the above formulæ.

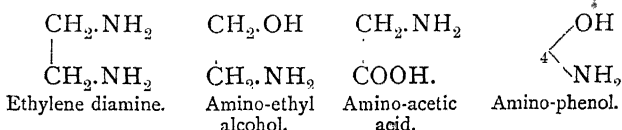


Analogous amido-derivatives, called *amides*, are obtained from acids. In these the electronegative or acidifying influence of oxygen, which is to be observed amongst all organic and inorganic compounds—for instance, from a comparison of the strong acid, nitric acid with the strong base ammonia,—is evident. Acetamide, the amide of acetic acid, has only very weak basic properties, its salts, such as acetamide hydrochloride, being decomposed by water. It contains the basic amino-group attached to the acid radical acetyl, and the influence of the latter is further shown in the fact that the amide can also function as an acid and have one of the hydrogen atoms in the amino-group replaced by a metal.

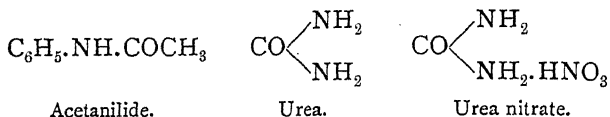


The corresponding derivatives of an aromatic amide such as benzamide,  $\text{C}_6\text{H}_5\text{CO}\cdot\text{NH}_2$ , have even a less marked basic character, but their acid properties are stronger; this is quite in accord with the electro-negative influence of the phenyl group.

The influence of other substituting groups containing oxygen is exactly similar. Thus, whilst compounds containing two amino-groups are, as would be expected, stronger bases than those containing one, the amino-alcohols are weaker bases than the amines. The amino-acids and the amino-phenols behave as both acids and bases, and both these characters are mutually weakened by the second substituting group present.

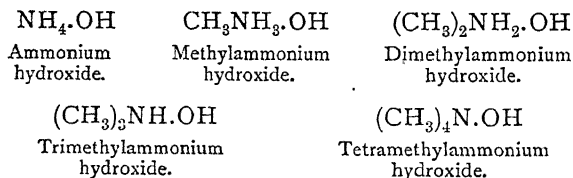


Similarly, *acetanilide* (antifebrine), in which the acetyl group is in combination with the radical of aniline, acts, like acetamide, both as a very weak acid and a very weak base, whilst urea, which contains two amino-groups, behaves in respect to its basic properties—*i.e.*, its power of forming salts—as if only one were present, owing to the acidifying influence of the contained carbonyl.



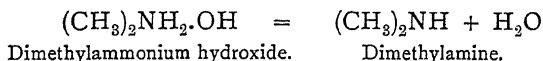
These general influences of the nature of the constituent groups of a molecule on its properties are of the utmost importance, both in drawing conclusions as to the structure of compounds and in practical laboratory work. The present knowledge of the subject is mainly qualitative, though it is probable that a more precise knowledge of the quantitative influence of substituents will gradually be acquired with the exact methods which are now available for the measurement of the strengths of acids and bases, and of the hydrolysis of their salts. The subject becomes especially complicated when a polyvalent element brings new valencies into play, as in the derivatives of nitrogen, phosphorus, arsenic, sulphur, iodine and oxygen, all of which can give rise to basic compounds under certain conditions of valency.

Some light is thrown on this problem by a consideration of the derivatives obtained by the successive replacement of hydrogen atoms in ammonium hydroxide by methyl groups. The following compounds are thus obtained:—

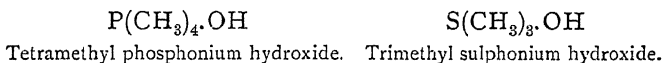


On comparing the relative strengths of these bases, it is found that the first four do not differ very markedly in this

respect; the addition of each methyl group adds somewhat to the basic character, but trimethylammonium hydroxide is still far less basic than the alkali hydroxides. Tetramethylammonium hydroxide, on the other hand, is incomparably stronger than any of the others. This marked difference is attributed to the fact that each of the other four is capable of splitting off water and forming a derivative of ammonia, whilst the tetramethyl compound cannot do so. Since the amines are basic only in the form of their hydroxy-compounds, the basic strength is naturally greatly diminished if the hydroxide can split off water and form the inert amine, *e.g.* :—



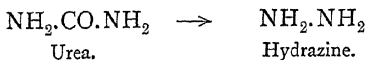
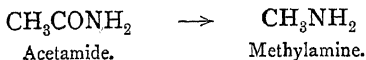
Similar considerations apply to the analogous basic derivatives of phosphorus and sulphur, the phosphonium and sulphonium compounds:—



Under certain circumstances oxygen can become quadrivalent and then assumes basic properties. By analogy with the ammonium compounds, the substances in which oxygen exerts this power are called *oxonium* compounds.

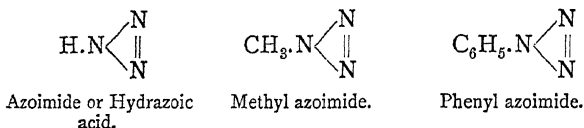
In concluding this reference to the organic derivatives of ammonia and allied compounds, it is interesting to note the services rendered by organic chemistry in the preparation of the other hydrides of nitrogen. *Hydrazine* or *Diamide*,  $\text{N}_2\text{H}_4$ , was first obtained from an organic compound, triazo-acetic acid, by Curtius in 1889. A remarkably simple synthesis of this substance, also from an organic compound, has been more recently discovered by Schestakow (1905). When acid amides are acted upon by a hypobromite, or hypochlorite, the group,  $\text{CONH}_2$ , is replaced by the amino-group; acetamide, for instance, gives methylamine, and this is the most convenient method for its preparation. By applying this reaction to urea, hydrazine is obtained, the CO group of the amide radical being similarly eliminated:—





Organic derivatives of hydrazine had been known long before. Phenyl hydrazine, discovered in 1875 by E. Fischer, has been of immense service in the study of the sugar group, and also in the synthesis of several valuable compounds, typically in that of antipyrine.

*Azoimide* or *Hydrazoic acid*,  $\text{N}_3\text{H}$ , was first prepared by Curtius in 1890, by the action of hydrazine upon ethyl hippurate. The phenyl derivative of this hydride of nitrogen has already been referred to, and methyl azoimide has been recently prepared for the first time by Dimroth and Wislicenus (1905):—



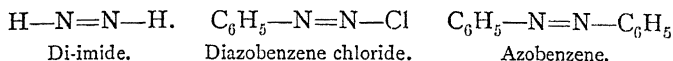
Two other hydrides of nitrogen, Buzylene or Diazo-hydrazine,  $\text{N}_4\text{H}_4$ ,<sup>1</sup> and Di-imide,  $\text{N}_2\text{H}_2$ ,<sup>2</sup> are as yet only known in their organic derivatives; further services of the organic chemist are the most likely means of inorganic chemistry being enriched by the discovery of the simpler mother substances.

*Compounds containing Nitrogen linked to Nitrogen. Diazo- and Azo-compounds.*—The organic derivatives of the nitrogen hydrides, azoimide and hydrazine, are also types of compounds containing nitrogen linked to nitrogen. The unknown di-imide,  $\text{N}_2\text{H}_2$ , similarly represents this condition of combination; it is to be regarded as the mother substance of the most important members of this class, the diazo- and azo-compounds. In the former, one of the nitrogen atoms is linked to an aryl

<sup>1</sup> Curtius, *Berichte*, 1893, xxvi. 1263; Wohl and Schiff, *Berichte*, 1900, xxxiii. 2741.

<sup>2</sup> Vaubel, *Berichte*, 1900, xxx. 1711.

radical, the second to that of an inorganic acid; in the latter, both are linked to aryl radicals.



The chief importance of these diazo- and azo-compounds is centred in the aniline colour industry. More than fifty per cent. of the aniline colours manufactured to-day fall into this group. They include almost every colour and shade from yellow, red, and brown to blue, violet, green, and black, and on account of their variety and stability these "azo-colours" are amongst the most valuable products of the colour manufacturer. The advances made in their preparation since their discovery in 1863 have been phenomenal, and there appears no limit to the adaptability and extension of the methods employed for their manufacture. There are but few important colours that are not derived from diazo- or azo-compounds, so that the development of this group constitutes to a very large extent the development of the coal-tar colour industry. Any attempt to record the brilliant successes that have been achieved in this branch of technical organic chemistry would lead far beyond the confines of this book; it will be only possible to indicate the nature of the reactions and compounds concerned, that have proved of value in the growth of the industry.<sup>1</sup>

The initial discovery on which the azo-colour industry is based was made by Peter Griess in 1860.<sup>2</sup> By the action of nitrous acid upon ice-cold aniline hydrochloride

<sup>1</sup> Details of the Aniline colour industry and of its historical development will be found in the following books and papers:—

J. C. Cain and J. F. Thorpe, *The Synthetic Dyestuffs and Intermediate Products*, 1895.

R. Meldola, *Coal and what we get from it*, 1891.

K. Heumann, *Die Anilinfarben und ihre Fabrikation*, 1888-1900.

R. Nietzki, *Chemie der organischen Farbstoffe*, fifth edition, 1906.

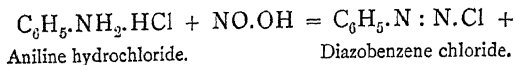
Sir W. H. Perkin, "Hofmann Memorial Lecture," *J. Chem. Soc.*, 1896, lxix. 596.

H. Caro, "Ueber die Entwicklung der Theerfarben Industrie," *Berichte*, 1892, xxv. 955.

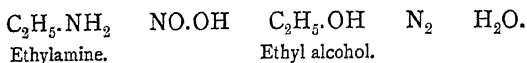
<sup>2</sup> "Ueber eine neue Klasse organischer Verbindungen in denen Wasserstoff durch Stickstoff vertreten ist," *Annalen*, 1860, cxiii. 201.

## MODERN ORGANIC CHEMISTRY.

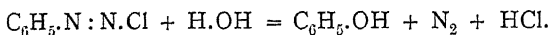
he prepared diazobenzene chloride, from which the first azo-dye, aniline yellow, was subsequently obtained by the further action of aniline (1863). This reaction with nitrous acid may be provisionally represented by the equation:—



It is a reaction that is restricted to primary aromatic amines, such as aniline and its homologues. Aliphatic amines undergo a more complete decomposition when acted upon by nitrous acid, forming the corresponding alcohols with liberation of nitrogen, thus:—



This further decomposition also takes place when an aqueous solution of the diazobenzene chloride is heated, and hence a low temperature is necessary for the preparation of the diazo-compounds; ice-cold solutions are always employed. The decomposition of a diazobenzene chloride solution, on heating, takes place according to the equation:—



The salts of diazobenzene are characteristically unstable, and when dry most of them are very highly explosive, a property to be attributed to the strained condition of combination between the two nitrogen atoms of the molecule. Associated with this instability are the numerous synthetical reactions, by means of these salts, which have been of paramount importance in the preparation and study of aromatic compounds. The "diazo-reactions" consist in the replacement of the diazo-grouping by a univalent element or radical, and there is hardly an important substituent that cannot be thus introduced into the benzene ring. Simple and direct laboratory methods are available for converting the diazobenzene salts into benzene, phenol, halogen derivatives, benzonitrile, thiophenol, and benzene sulphonic acid; in all these changes the nitrogen of the diazo-group is liberated, as shown in

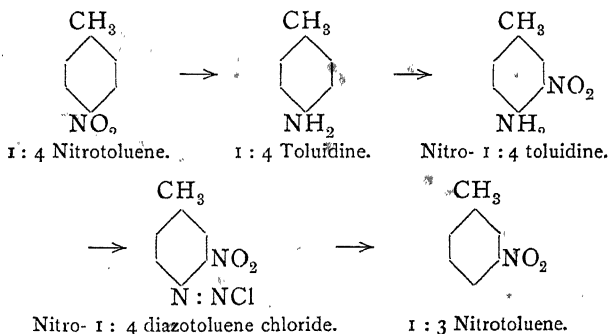
the above equation representing the formation of phenol from diazobenzene chloride.

$C_6H_5.N : N.Cl.$  (*Diazobenzene chloride*) gives:—

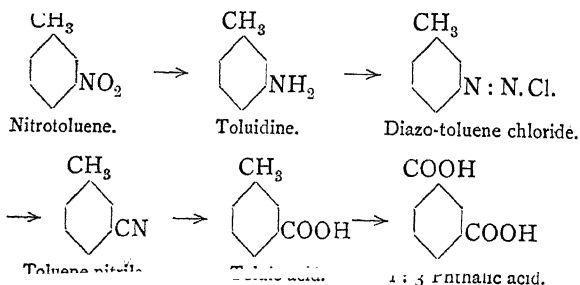
$C_6H_6.$ Benzene.	$C_6H_5.OH.$ Phenol.	$C_6H_5.Cl.$ Chlorbenzene.	$C_6H_5.Br.$ Brombenzene.
$C_6H_5.I.$ Iodobenzene.	$C_6H_5.CN.$ Benzonitrile.	$C_6H_5.SH.$ Thiophenol.	$C_6H_5.SO_2OH.$ Benzene sulphonic acid.

The formation of phenol takes place on simply warming. For the preparation of benzene, a reducing agent such as alcohol or sodium stannite is required. Most of the other reactions are effected by the catalytic action of cuprous salts or of finely divided copper powder, the nitrogen being in all cases liberated in the form of gas.

All homologues and substitution products of diazobenzene salts show a similar reactivity and diazo-reactions are consequently employed in the most varied directions, both for preparing aromatic compounds and for deciding their orientation. For instance, meta-nitrotoluene cannot be prepared directly from the hydrocarbon, the para-compound being the chief product obtained by direct nitration. This can, however, be made use of for the preparation of meta-nitrotoluene by first reducing it to para-toluidine, nitrating the latter, then diazotising the contained amino-group, and finally replacing the diazo-group by hydrogen. The following formulæ represent these changes:—



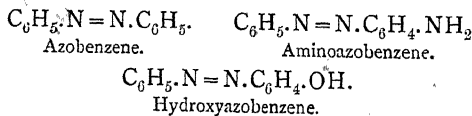
In order to carry out this preparation in practice, it is necessary to protect the amino-group before nitrating, by introducing an acetyl group. That the resulting nitro-toluene is a meta-compound can be proved by converting it into meta-phthalic acid, a compound of proved orientation. This conversion involves the reduction of nitro-group, the diazotizing of the resulting amine, then the replacement of the diazo-group by cyanogen, the saponification of the resulting nitrile, and finally the oxidation of the side-chain to carboxyl, thus:—



Series of changes of this type have been widely employed in the study of aromatic compounds; in very many cases, diazo-reactions supply the important link from the known to the unknown, or vice versa.

A further series of diazo-reactions, in which the nitrogen of the diazo-group remains intact, leads to the preparation of the technically important azo-dyes.

Azo-benzene itself is a bright red compound, but it does not permanently colour animal or vegetable fibre, hence it is not a dye. By the introduction of certain salt-forming groups into the molecule dyes result; the amino- and hydroxy-groups are the most important of these substituents or *auxochromic* groups, and the two chief classes of azo-dyes are typified by aminoazobenzene and hydroxyazobenzene respectively:—

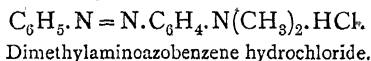
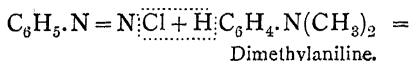
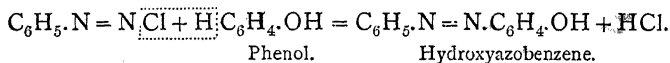


Most dyes contain one or more of such salt-forming groups, associated with a colour-forming group or *chromophore*,—in this case the azo-radical  $\text{—N=N—}$ . Compounds containing such a chromophore, but no auxochromic groups have been termed *chromogens*; like azo-benzene they may be coloured, but they are not dyes. Similar relations exist amongst other organic dyes.

<i>Chromophore</i>	$\text{—N=N—}$	<i>Azo-radical.</i>
<i>Chromogen</i>	$\text{C}_6\text{H}_5\text{—N=N—C}_6\text{H}_5$	<i>Azobenzene.</i>
<i>Dye</i>	$\text{C}_6\text{H}_5\text{—N=N—C}_6\text{H}_4\cdot\text{NH}_2$	<i>Aminoazobenzene.</i>

Certain coloured substances which contain no salt-forming groups, such as indigo, are used as dyes. These are, however, not applied direct to the fibre, but are converted into soluble reduction products which are brought on to the fibre and then oxidised, and thus deposit the insoluble dye on the cloth.

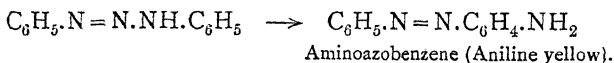
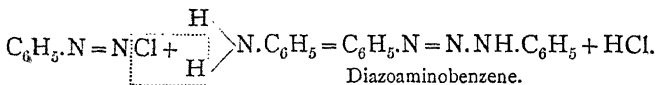
The formation of azo-dyes from the salts of diazobenzene and its homologues or derivatives takes place by means of certain *addition* or *coupling reactions*. Phenols and mixed tertiary amines (amines containing both alkyl and aryl radicals), react directly, according to the following equations:—



In both cases the chlorine of the diazo-chloride combines with a hydrogen atom of the benzene ring to form hydrochloric acid, whilst the phenol or amine residue becomes linked to the azo-chromophore.

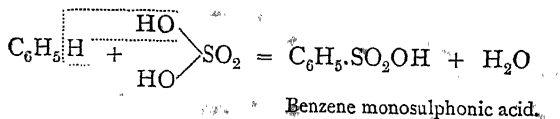
An indirect coupling reaction leads to the formation of azo-colours on somewhat different lines. Aniline and other primary aromatic amines couple with diazobenzene chloride, for instance, to form diazo-amino compounds, in which the hydrogen of the amino-group, instead of that of the benzene ring, reacts with the chlorine of the diazo-

chloride. The resulting compounds are almost colourless when pure, and have no tinctorial power; but when warmed in presence of a trace of an amine salt, they undergo a peculiar molecular change with the formation of aminoazo-compounds. These changes may be represented by the equations:—



The part played by the amine salt is not indicated in the equation representing the molecular change from diazoaminobenzene to aminoazobenzene; it appears to act catalytically as an accelerator of the reaction, the change itself having been proved to be uni-molecular.<sup>1</sup>

The technical value of organic dyes is, in most cases, influenced by their solubility in water, as this property greatly facilitates their practical application. Very many azo-colours are sparingly soluble in water, and in order to render them soluble, advantage is taken of the fact that all benzenoid hydrocarbons and their derivatives are readily converted into sulphonic acids by the direct action of concentrated sulphuric acid; the salts of these sulphonic acids are soluble in water. This method for converting an insoluble aromatic compound into a soluble derivative has received numerous important applications in the aniline colour industry;<sup>2</sup> it may be typified by the formation of benzene sulphonic acid from benzene, according to the equation:—



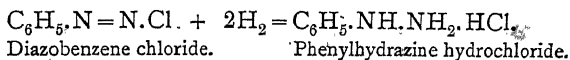
<sup>1</sup> H. Goldschmidt and R. Reinders, *Berichte*, 1896, xxix, 1369 and 1899.

<sup>2</sup> Cf. Caro, "Über die Entwicklung der Theerfarben Industrie," *Berichte*, 1892, xxv, 1,005.

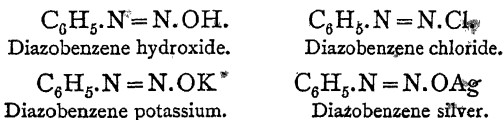
The technically important azo-colours are more complex than the above compounds, which have been selected to illustrate the general methods of preparation. They are derived not only from benzene, but also from other cyclic hydrocarbons, such as naphthalene and diphenyl, and are built up with a full knowledge of the relation of colour to the number and position of the auxochromic groups introduced.

The azo-colours form but one branch of the aniline industry. Other derivatives of cyclic compounds lead to the rosanilines, eosines, safranines, indulines, etc., artificial alizarin and indigo; a number of colours are known amongst aliphatic compounds, but none of them are of technical importance, except those in which the aliphatic radicals are combined with cyclic groups.

*The Structure of Diazo-compounds.*—The provisional structure for diazobenzene chloride, employed in all the reactions given above, was suggested by Kekulé (1866), in place of a previous formula assigned by Griess, the incorrectness of which was satisfactorily proved. Kekulé's formula leads to a clear expression of all the typical diazo-reactions; it affords a simple representation of the formation of diazo-salts from primary amines and is supported by their ready reduction to hydrazines:—

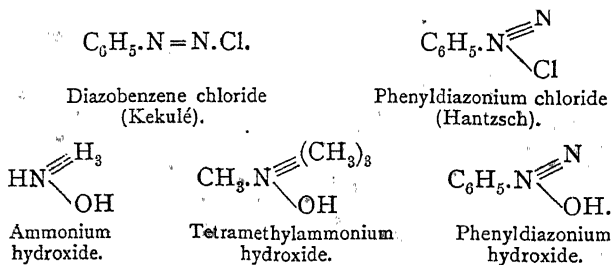


In addition to the compounds in which the diazo-grouping is attached to an acid radical, a number of metallic diazo-compounds are known, such as potassium and silver diazobenzene. The former is prepared by the action of potassium hydroxide on diazobenzene chloride, and the silver salt is obtained as an amorphous, explosive substance, by adding silver oxide to a solution of a diazo-salt. Like the diazo-chloride, these were regarded as derived from diazobenzene hydroxide, the mother-substance of the group, and until 1894 the Kekulé formula was generally accepted, both for the hydroxide and for all its derivatives:—





For a number of years past there has been very considerable controversy concerning the structure of diazo-compounds, the scope of which has been much extended and complicated by the discovery of many new diazo-derivatives and of new reactions bearing on their preparation and decompositions. Opinion is still divided on several points connected with the problem, but the investigations of Hantzsch and of Bamberger<sup>1</sup> have proved that one and the same structure cannot be accepted for all diazo-compounds, and that the Kekulé formula is not consistent with the general character of the diazobenzene salts of strong mineral acids, such as hydrochloric, nitric, and sulphuric. These latter salts resemble ammonium and organic ammonium salts<sup>2</sup> in their physical properties; they are electrolytically dissociated in solution, and are neutral, like the salts of a strong base. Hence, it is concluded that they contain a quinquevalent nitrogen atom, instead of the second tervalent nitrogen atom in the Kekulé formula, and that the mother-substance is a strong base, similarly constituted to ammonium hydroxide. By analogy, the terms *diazonium salts* and *diazonium hydroxide* are now used in place of diazobenzene chloride, etc. These relations are shown in the following formulæ:—

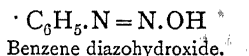
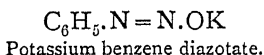


The metallic derivatives of diazobenzene, now called *diazotates*, are regarded as having the structural formula

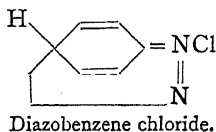
<sup>1</sup> Cf. "The Chemistry of the Diazo-Compounds," J. C. Cain, 1908. Also, G. T. Morgan, "Our Present Knowledge of Aromatic Diazo-compounds," *British Association Reports* 1902, p. 181; and Hantzsch, "Die Diazoverbindungen," *Sammlung chem. und chem.-technischer Vorträge*, 1902.

<sup>2</sup> Cf. this chapter, p. 202.

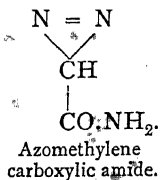
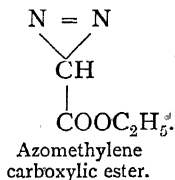
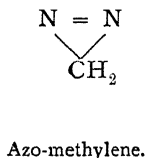
assigned by Kekulé, and in order to account for the existence of certain isomers that have been obtained as a result of the extended study of this group, Hantzsch has sought the aid of stereochemical isomerism.<sup>1</sup> That phenyldiazonium hydroxide, a strong base, should react with alkalis to form salts, thus acting as an acid, is contrary to the behaviour of strong bases in general, and it is probable that an intramolecular change occurs, and that this latter function is only exerted in the form of the isomeric diazo-hydroxide:—



J. C. Cain<sup>2</sup> has recently suggested entirely different formulæ for the diazo-compounds, which appear to be supported by many of their properties and reactions; the structural formula proposed for diazobenzene is as follows:—



Despite many attempts, no true diazo-compounds have been prepared\* in the aliphatic group, but aliphatic azo-compounds are known. These were first studied by Curtius, who obtained many derivatives of azo-methylene, and they were the compounds that led to the successive isolation of hydrazine and azoimide (1889). More recently azo-methylene itself has been prepared by von Pechmann (1894); it is a poisonous, yellow gas.

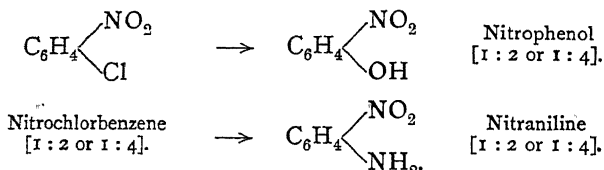


<sup>1</sup> Cf. Chap. xii., p. 322.

<sup>2</sup> *J. Chem. Soc.*, 1907, xci. 1049.

*Empirical Laws of Substitution in Benzenoid Compounds.*

—Reference has already been made to the fact that the properties and chemical behaviour of compounds are influenced by the position of the substituting groups or elements in the molecule;<sup>1</sup> this subject has been very fully studied in the case of the di-substitution products of benzene. In general, ortho- and para-compounds show many points of similarity, and behave differently from the corresponding meta-compounds. For instance, ortho- and para-quinones are known,<sup>2</sup> but analogous meta-quinones appear to be incapable of existence. Further, the preparation of azoimide from the nitro-derivative of phenyl-azoimide, referred to above, by the action of caustic alkalis can only be effected when the nitro-group is in the ortho- or para-position to the azoimide radical; the meta-compound is not attacked. Similarly, the chlorine in ortho- and para-nitrochlorbenzene is replaced by the hydroxyl- or amino-group when treated with potassium hydroxide or with ammonia respectively, but the meta-compound is again stable towards these reagents:—



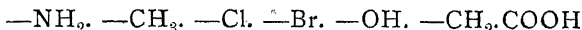
These changes are also of interest because they illustrate the influence of the nitro-group on the stability of the chlorine in the molecule, since this element is not normally substituted by the above reagents in aromatic compounds.<sup>3</sup>

The similarity in the behaviour of ortho- and para-compounds is more fully emphasised in what are known as the *Empirical laws of Substitution* in benzenoid compounds. The study of the formation of di-substitution products has led to the recognition of certain regularities which are not only of practical value in the preparation of compounds, but which contribute also important theoretical considerations in respect to the structure of benzene.

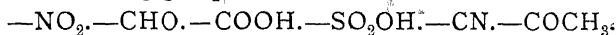
<sup>1</sup> Chap. viii. p. 155.<sup>2</sup> Cf. Chap. xv. p. 418.<sup>3</sup> Cf. ante. p. 199.

Noelting<sup>1</sup> and Armstrong<sup>2</sup> were, independently, the first to draw attention to these regularities, which were subsequently expressed in a more definite form by Crum Brown.<sup>3</sup> When a mono-substitution product of benzene,  $C_6H_5X$ , is converted into a di-substitution product,  $C_6H_4XY$ , the resulting compound is either a mixture of ortho and para [1 : 2 and 1 : 4] in varying proportions according to the conditions of the experiment, or else almost exclusively meta [1 : 3]. The position of the new substituent depends almost entirely upon the nature of  $X$ ; it is practically independent of the nature of  $Y$ . The substituents  $X$  thus fall into two groups, of which the following are the most important members, in respect to their directing influence on the position taken by  $Y$ :—

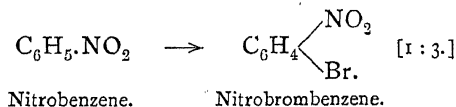
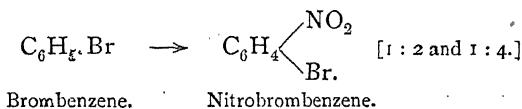
I. *Ortho-para orienting groups*:—



II. *Meta-orienting groups*:—



Thus, when brombenzene is nitrated, a mixture of ortho- and para-nitrobrombenzene results, whilst nitrobenzene yields the meta-compound when brominated:—



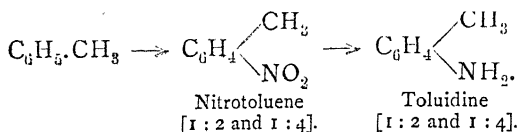
The preparation of the three toluidines and of the three nitrobenzoic acids afford good instances of the practical application of these empirical laws. Ortho- and para-toluidine (amino-toluene) are readily accessible from the hydrocarbon (toluene), since the latter yields the ortho- and para-nitrotoluenes upon nitration, from which the

<sup>1</sup> *Berichte*, 1884, xvii. 261.

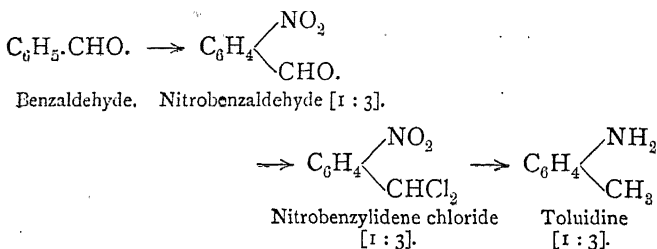
<sup>2</sup> *J. Chem. Soc.*, 1887, li. 258.

<sup>3</sup> *Ibid.*, 1892, lxi. 368.

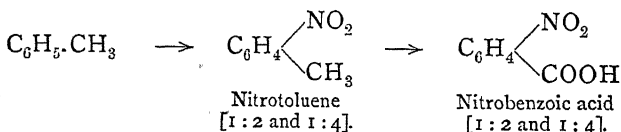
corresponding amino-compounds are obtained by reduction:—



An indirect method is required for the preparation of the meta-compound, and in making a selection of the possible reactions that might be employed it is necessary to look for a compound containing a meta-orienting group which can be replaced by the desired substituent. Benzaldehyde fulfils these conditions. When nitrated the meta-nitro-compound is formed, from which the corresponding toluidine can be obtained by the action of phosphorus pentachloride and subsequent reduction:—



Benzoic acid, on the other hand, yields the meta-compound by direct nitration, and indirect methods must be employed for the preparation of the isomers. Since the  $\text{CH}_3$  group is an ortho-para orienting group, and can be readily oxidised to carboxyl, toluene is obviously a suitable starting-point, as indicated by the following changes:—



These examples suffice to show the general method adopted to introduce a substituent into any desired

position; it consists in the application of the empirical laws combined with the reactions which serve for the mutual replacement of substituting groups.

In respect to the theoretical considerations arising out of these laws it is to be noted, as was first pointed out by Armstrong, that the substituents in the Groups I. and II. differ in their chemical behaviour, especially in the power possessed by the meta-orienting groups of forming addition compounds, a property already considered in the case of aldehydes,<sup>1</sup> the typical radical of which is included in this group. This difference has led to the suggestion that, assuming substitution to be preceded by addition, this addition takes place with the substituent already present in the molecule in the formation of meta-compounds and with the carbon atom, to which the substituent is subsequently attached, in the formation of ortho- and para-compounds. The fact that the amino-group and its substitution products sometimes function as meta-orienting groups is attributed, on this view, to the possibility of either method of addition.

Although this difference in the chemical behaviour of the two groups is well founded, the mechanism of substitution is as yet too hypothetical to allow of any general theoretical deductions from these empirical laws of substitution. These laws and the difference in the behaviour of meta- in contradistinction to ortho- and para-compounds both show that there is a constitutional difference in these two classes of benzenoid substitution products, and no formula for benzene can be regarded as satisfactory which does not give a due interpretation of this difference. Neither the Kekulé nor the centric formula gives any indication of this "meta-law." "Space formulæ" devised by Collie and others offer some suggestion of a difference in structure of meta- as compared with ortho- and para-compounds, but they give only a hypothetical explanation of the changes that may lead to meta- or to ortho-para-substitution.<sup>2</sup>

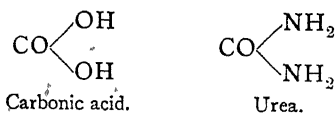
*Uric Acid and Allied Compounds.*—Urea, hippuric acid,

<sup>1</sup> Chap. viii. p. 137.

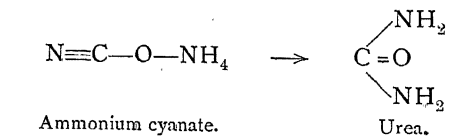
<sup>2</sup> Cf. Collie, *J. Chem. Soc.*, 1897, lxxi. 1018; Lapworth, *J. Chem. Soc.*, 1898, lxxiii. 454; Marsh, *J. Chem. Soc.*, 1902, lxxxi. 961; Barlow and Pope, *J. Chem. Soc.*, 1906, lxxxix. 1697.

and uric acid are the chief nitrogenous excretory products of animal metabolism. They are derived from the complex proteins contained in the various tissues and fluids of the body, and constitute, together with ammonia, the decomposition products of the nitrogen of food. In the case of mammals, by far the largest proportion of the excreted nitrogen leaves the body in the form of urea; a minor proportion is eliminated as uric acid. With birds and reptiles uric acid takes the place of urea, whilst the herbivora excrete both hippuric and uric acids. It appears that the liver is the chief centre of this oxidation of the nitrogenous constituents of the body, and there are, beyond doubt, many stages that intervene between the complex compounds conveyed to the liver by the blood and these final products of their metabolism. There is but little certain knowledge regarding these intermediate products. The total change is one of oxidation from less to more highly oxidised compounds successively; uric acid is probably a forerunner of urea, and experiments by Araki<sup>1</sup> indicate that the formation of ammonium lactate precedes that of urea.

Urea is an acid amide derived from carbonic acid, and it is of interest to note that, whilst the carbon of food is oxidised in the body to carbonic acid, the nitrogen yields a compound of similar type.—



Urea was first prepared synthetically by Wöhler in 1828, by heating ammonium cyanate; the change involves a complex molecular rearrangement, as is evident from the structural formulæ of the respective compounds:—

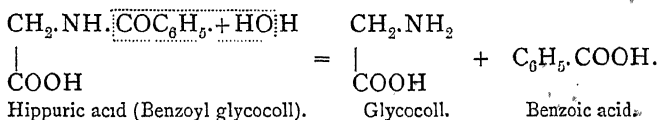


<sup>1</sup> *Z. physiolog. Chem.*, 1891, xv. 335.

Urea is formed either by heating a solution of ammonium cyanate or by melting the solid, and the reaction has been shown to be reversible;<sup>1</sup> it reaches a limit which at 100° in aqueous solution, corresponds to a mixture containing about 91.6 parts of urea to 4.5 parts of ammonium cyanate, some four per cent. of the products being lost owing to secondary decompositions. A mixture of the same composition is formed when a solution of urea is heated to the same temperature; it represents, therefore, a condition of equilibrium analogous to that observed in the preparation of ethereal salts.<sup>2</sup>

The historic importance of Wöhler's synthesis, the first recognised attack on the "vital force" distinction between organic and inorganic compounds, may be recalled. Numerous other syntheses of urea are now known which leave no doubt as to its structure.

*Hippuric acid* is also a comparatively simple compound. It is derived from amino-acetic acid, one hydrogen atom of the amino-group being replaced by the benzoyl radical. This is proved by the formation of amino-acetic acid (glycocoll or glycine), and benzoic acid upon hydrolysis with alkalis or acids; also by various synthetical methods of preparation:—



Hippuric acid is eliminated in human urine after ingestion with benzoic acid or with other simple derivatives of benzene.<sup>3</sup>

*Uric acid* and its allies, on the other hand, belong to a very complex group of compounds, and it is only within the last few years that their structure has been completely elucidated. The members of this group are in part of animal, in part of vegetable origin. *Paraxanthine* and *heteroxanthine* are associated with uric acid in urine; *xanthine*, *adenine*, and *hypoxanthine* are found in the

<sup>1</sup> Walker, *J. Chem. Soc.*, 18 5, lxvii. 746; 1897, lxxi. 489; 1900, lxxvii. 21.

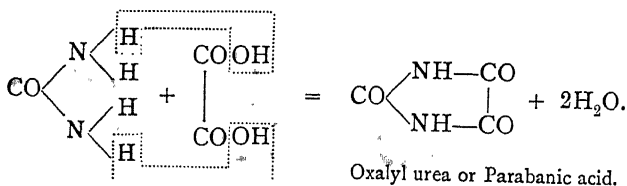
<sup>2</sup> *Cf.* Chapter ix., p. 163.

<sup>3</sup> *Cf.* Chap. xvi. p. 453.

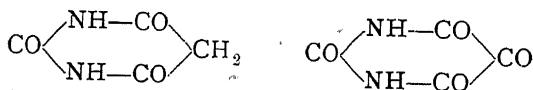


pancreas, spleen, and liver, and probably form part of the nucleins of cells, whilst *theobromine*, *caffèine*, and *theophylline* are products of vegetable metabolism, being the physiologically active constituents of tea, coffee, and cocoa. The foundation of the present knowledge of this group was laid by Liebig and Wöhler in a classical memoir, "Investigations on the nature of Uric Acid," published in 1838.<sup>1</sup> In this paper very many derivatives of uric acid were described, and their mutual relations studied with a degree of accuracy which has permitted neither additions nor corrections. The synthetical stage in the study of the group was first approached by von Baeyer (1863), who succeeded in preparing several of the decomposition products of uric acid obtained by Liebig and Wöhler, but who fell just short of the synthesis of the acid itself. Emil Fischer in 1896 supplied the coping-stone to Baeyer's work, and has since successfully extended his studies to the whole of the uric acid group.

Urea itself is the simplest starting point for the consideration of these compounds. The simpler organic acids react readily with urea, in presence of a suitable dehydrating agent, to form heterocyclic compounds known as *Ureïdes*. Thus oxalic acid forms oxalyl urea according to the equation:—

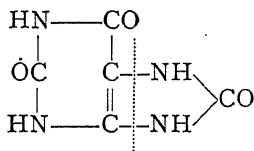


Malonyl urea, or "barbituric acid," and mexoxalyl urea, or "alloxan," are similarly derived from malonic and mesoxalic acids respectively.



<sup>1</sup> "Untersuchungen über die Natur der Harnsäure," *Annalen*, 1838, xxvi. 241.

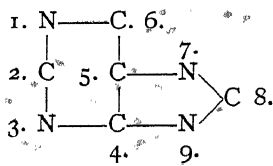
All these compounds were originally prepared from uric acid by Liebig and Wöhler, to whom the alternative names of parabanic acid, barbituric acid and alloxan are due; they were subsequently obtained synthetically by von Baeyer. Since uric acid forms urea and alloxan upon oxidation it was regarded as a simple ureide in combination with a urea radical, and as long ago as 1875 Medicus suggested a formula for it which has since been proved to be correct:—



Uric acid. (Medicus.)

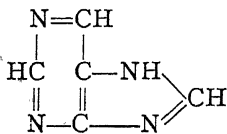
The formation of alloxan and urea upon oxidation is completely in accord with this formula, the decomposition taking place at that portion of the molecule indicated above by the dotted line. But alternative formulæ are possible, and it was not until Emil Fischer (1884) showed the existence of two monomethyluric acids, one of which gave alloxan and methylurea, the other methylalloxan and urea upon oxidation, that the correctness of this unsymmetrical formula was fairly established.

The correlation of the structure of the various members of the uric acid group, which has followed from Emil Fischer's later work (since 1895), has established the presence of the following atomic grouping in them all, the relative position of the atoms being denoted by the numbers 1 to 9:—



The simplest member of this group, the mother-substance of uric acid and its allies, is derived from the above nucleus by the addition of four atoms of hydrogen.

Fischer<sup>1</sup> has succeeded in preparing this compound, and has named it *Purine*, from *purum uricum*. Uric acid compounds are now classed as the purine group.

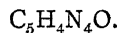


Purine.  $\text{C}_5\text{H}_4\text{N}_4$ .

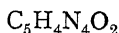
The empirical formulæ for purine, hypoxanthine, xanthine and uric acid differ successively by one atom of oxygen:—



Purine.



Hypoxanthine.

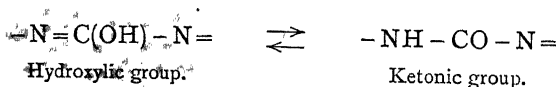


Xanthine.

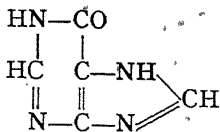


Uric acid.

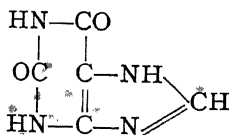
Each stands, therefore, in the empirical relation of a hydroxy-compound to its hydrocarbon, in respect to purine; hypoxanthine is related as a monohydroxy-derivative, xanthine and uric acid as di- and trihydroxy-derivatives respectively. This connection has been fully established by experiment. In order to make it clear, it is necessary to employ alternative hydroxylic and ketonic formulæ for these hydroxy-derivatives, as in the case of ethylacetate and phloroglucinol.<sup>2</sup>



The following formulæ represent these relations for hypoxanthine, xanthine and uric acid:—



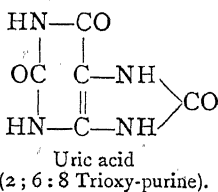
Hypoxanthine  
(6 Oxy-purine).



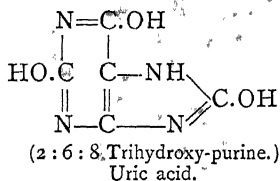
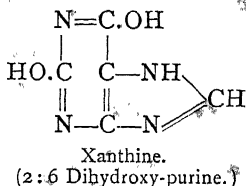
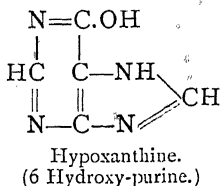
Xanthine  
(2:6 Dioxy-purine).

<sup>1</sup> *Berichte*, 1899, xxii, 449.

<sup>2</sup> Cf. Chap. xiv., p. 398.



*Alternative isomeric formulæ:—*

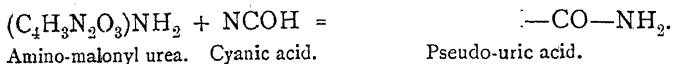
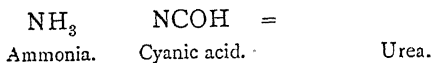


These isomeric relations are necessary for the consideration of the synthetical reactions employed by Emil Fischer in the study of the purine group, reactions which have led to the preparation of no less than some 200 purine compounds, and to a full proof of the position occupied by the various substituents in the purine ring. Full details of this work will be found in Fischer's summary of his investigations;<sup>1</sup> it must suffice here to indicate briefly the methods employed.

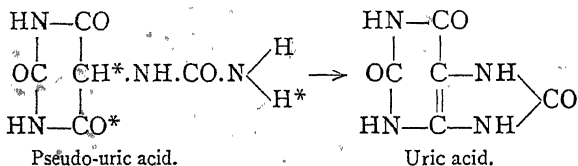
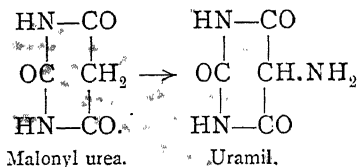
Von Baeyer had prepared a compound known as pseudo-uric acid by the action of potassium cyanate on aminomalonyl urea or tramil, the ureide of malonic acid, in which a hydrogen atom in the  $\text{CH}_2$  group is replaced by the amino-group. The reaction is analogous to the synthesis

<sup>1</sup> "Die Puringruppe," *Berichte*, 1899, xxxii. 435; "Untersuchungen in der Puringruppe" (1882-1906), 1907.

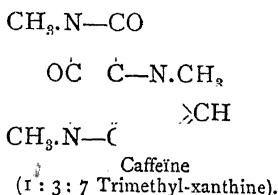
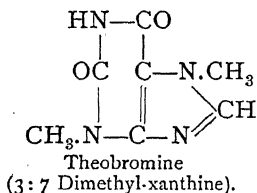
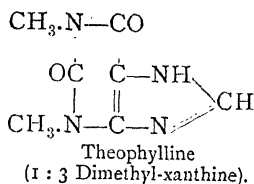
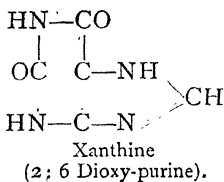
of urea from ammonium cyanate, as shown in the following equations:—



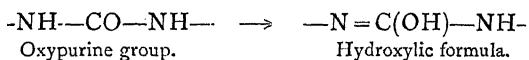
This pseudo-uric acid differs in composition from uric acid by the elements of a molecule of water, which Fischer found could be removed by the action of dilute hydrochloric acid with the formation of uric acid:—



The two hydrogen atoms and one oxygen atom eliminated from the pseudo-acid as water are marked with asterisks. The importance of this reaction lies in the fact that many methyl derivatives of pseudo-uric acid can be similarly prepared, which thus lead to the synthesis of methyl uric acids; and since the position of the methyl groups in the pseudo-acids is determined by the compounds used in the synthesis, their position in the purine ring can be established. These methyl derivatives include theophylline, theobromine, and caffeine, and the orientation of these compounds (which can also be obtained by the direct methylation of xanthine) has been in part established by this method.

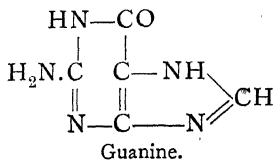
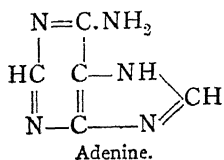


A second method employed by Fischer has led to the successive reduction of uric acid to xanthine, hypoxanthine, and finally to purine itself. This reduction cannot be effected directly, but by first allowing phosphorus oxychloride to act upon the oxypurines, chlorpurines are formed, which can be reduced. The changes involved are best represented on the hydroxylic formula<sub>s</sub> of the oxypurines:—



On these lines the methyl uric acids can be converted into methyl-xanthines, and the latter, by a repetition of these changes, into the methyl-hypoxanthines; or, by reducing uric acid itself to xanthine or hypoxanthine, and methylating the latter, theophylline, theobromine, and caffeine can be prepared from uric acid as the starting-point. The chlorpurines are very reactive compounds; when treated with aqueous alkali or acid the chlorine atom is replaced by hydroxyl, thus leading back to the oxypurines themselves; and by suitable reagents the halogen can be substituted by the groups  $\text{OC}_2\text{H}_5$ ,  $\text{SH}$ ,  $\text{NH}_2$ , with the formation of purine ethers, thiopurines, and aminopurines.

The latter include adenine, which is 6 amino-purine, and, therefore, closely related to hypoxanthine and guanine, which is 2 amino-hypoxanthine:—



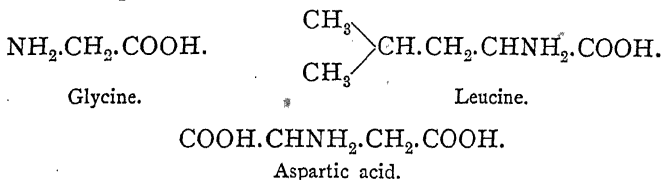
The therapeutic importance of theobromine and caffeine adds a special interest to this remarkable series of investigations. Uric acid is a readily accessible compound, being contained in considerable quantities in guano, and since several methods are available for converting it into methylated dioxypurines; such as theophylline and caffeine, the commercial preparation of the latter from uric acid is already being effected. Further, the study of the relation of chemical structure to physiological action may reveal other compounds of therapeutic value amongst the now numerous members of the purine group.

*The Polypeptides.*—The term "Polypeptides" has been given by E. Fischer to a number of synthetically prepared compounds which are related to the proteins and to their products of decomposition. On account of the great importance of the part played by the proteins in animal and vegetable metabolism, a very special interest centres in the attempts that have been made to unravel the nature of these complex molecules.

Owing to the colloidal nature of these substances, referred to above, the differentiation of the natural products is difficult, and, as yet, in many respects unsatisfactory; but it has been possible to distinguish some forty or fifty natural proteins by means of such physical characteristics as solubility, coagulability, and the like. In order to gain an insight into their structure, both analytical and synthetic methods have been applied, the latter having naturally succeeded the former, as in the investigation of all other groups of organic compounds. Of the many analytical or decomposition processes that have been tried, that of hydrolysis<sup>1</sup> has hitherto been the only one to give useful

<sup>1</sup> Cf. Chapter ix. pp. 168, 173.

results. By the hydrolytic action of chemical reagents and of enzymes the proteins are successively broken down into albumoses and peptones, and finally into simpler compounds, amongst the most characteristic of which are certain amino-acids, such as amino-acetic acid or glycine, amino-isobutylacetic acid or leucine, and amino-succinic acid or aspartic acid:—



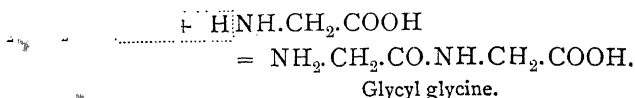
Some twenty different amino-acids have been obtained by this hydrolytic decomposition of the proteins; they include both aliphatic and cyclic compounds, and although the majority of them are always formed by the decomposition of all the typical proteins, the relative proportions obtained vary considerably.

These acids have very naturally been the starting-point for the synthetical experiments in this group of compounds. The products obtained in the earlier attempts to prepare protein-like compounds from such amino-acids were indefinite colloidal substances, which whilst they showed some of the empirical characteristics of the proteins, such as the "Biuret reaction" (the formation of a violet coloration on the addition of copper sulphate and sodium hydroxide), were products of unknown constitution, and consequently in no way helpful as a means of determining the structure of the group.

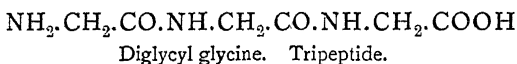
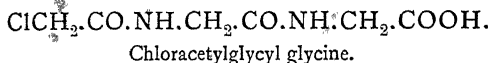
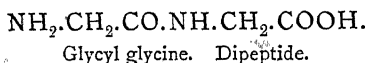
During the last few years, however, a great impetus has been given to the study of these compounds by the investigations of Emil Fischer, who has, since 1901, prepared a whole series of derivatives of amino-acids of known structure, which show many of the characteristics of the proteins, both in their behaviour towards enzymes and towards chemical reagents. Several reactions have been made use of by Fischer in these investigations, of which the following may be taken as a type. A substance called glycine or glycocoll (amino-acetic acid) anhydride was



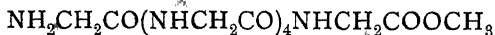
prepared by Curtius, which Fischer converted into a kind of double glycine molecule, glycyl-glycine, which may be regarded as derived from two molecules of glycine by the elimination of a molecule of water:—



Regarding the glycine radical as the representative of a peptide group, glycyl glycine is the simplest example of a *di-peptide*. By the successive action of the acid chloride of chloracetic acid and of ammonia on this compound, the corresponding *tri-peptide* can be obtained; the stages in these reactions are shown in the following formulæ:—



By a peculiar condensation, this tri-peptide can be converted directly into a *hexa-peptide*. Its methyl ester is first prepared, and this readily loses methyl alcohol on heating to 100°, forming pentaglycyl glycine methyl ester:—



By a further series of somewhat analogous reactions the chain of amino-acid residues may be further built up, and since the yields do not appear to decrease with the complexity of the compounds formed, as is usually the case in such repetitions of a synthetical process, the preparation of substances of a high degree of complexity may be expected. Fischer<sup>1</sup> has recently succeeded in preparing a compound of this group containing no less than eighteen of these amino-acid residues, an *octadeca-peptide*, which has a molecular weight of 1,213. As compared with the

<sup>1</sup> *Berichte*, 1907, xl. 1754.

proteins these polypeptides are doubtless simple molecules, but the systematic character of the reactions employed in their preparation mark a definite step towards elucidating the structure of the natural products, and Fischer's researches must accordingly be regarded as marking a new epoch in physiological chemistry.<sup>1</sup>

<sup>1</sup> Details of Professor Fischer's work and of the chemistry of the proteins will be found in the following books and papers:—

E. Fischer, "Untersuchungen über Aminosäuren, Polypeptide und Proteine, *Berichte*, 1906, xxxix. 530; and Faraday Memorial Lecture, *J. Chem Soc.*, 1907, xci. 1,757.

R. H. Aders Plimmer, "The Work of Emil Fischer and his School on the Chemistry of the Proteins," *Science Progress*, July 1907.

G. Mann, *Chemistry of the Proteids*, 1906.

S. B. Schryver, *Chemistry of the Albumens*, 1906.

A. Kossel, "Über den gegenwärtigen Stand der Eiweisschemie," *Berichte*, 1901, xxxiv. 3214.

## CHAPTER XI.

### THE LABORATORY METHODS OF ORGANIC CHEMISTRY.

The study of Reactions. Synthetical and Analytical experiments.

- I. *Methods for the Preparation of Organic Compounds*.—The preparation of monobrombenzene—Halogen carriers—Regulation of the temperature of reactions; the use of solvents—The preparation and isolation of solids; the preparation of acetanilide—Crystallisation—Filtration—Drying—Reactions with the chlorides of phosphorus; the preparation of acetyl chloride—The preparation of ethereal salts; ethyl acetate—The preparation of ethylacetoacetate—The use of metallic compounds in the synthetical preparation of organic compounds; compounds of zinc and of magnesium; the preparation of benzoic acid by the Grignard reaction.
- II. *Methods for ascertaining the Chemical Nature of Organic Compounds*.—The recognition of typical groups—Acids—Bases—Ethereal salts—Aldehydes and Ketones.
- III. *Oxidation and Reduction*.
- IV. *The application of Electrolysis to the preparation of Organic Compounds*.—The theory of electrolytic dissociation—The electrolytic preparation of para-aminophenol.

ORGANIC and inorganic chemistry are distinguished not only by the material with which they deal, but also by the methods of investigation employed, although a great many similar laboratory processes are naturally in daily use in all chemical work, in addition to the distinctive methods of experiment.

The laboratory methods of inorganic chemistry are extremely varied, owing to the stability of inorganic compounds and the wide range of temperature that can be employed in their study. The methods for the preparation and investigation of organic compounds, on the other hand, are, for the most part, more limited in range and more general in character; the latter characteristic is the outcome of the numerous synthetical reactions which play

so prominent a part in organic chemistry.<sup>1</sup> A distinctive feature in the practical study of organic chemistry is the fact that each reaction is almost invariably accompanied by subsidiary reactions; hence the yield of the desired product is practically never equal to that calculated from the equation expressing the reaction. This contrast to the conditions which obtain in reactions with inorganic substances is due to the many possibilities in the nature of the reactions which can occur. For this reason it is important always to record the yield of the product obtained, and one of the chief problems of the organic chemist, especially when working on technical problems, is to ascertain the conditions which will give the maximum yield of the desired compound.

The examination of a reaction between any two or more substances involves first of all the study of the conditions under which the reaction will proceed; secondly, the separation of the product or products of the reaction; and finally, the determination of their identity or of their composition.

Of these three processes, the last is similar in all cases. The physical properties described in Chapter VI. are employed for establishing the identity of known compounds, and their ultimate composition is ascertained by the ordinary methods of organic analysis.

The separation of the products of a reaction is conducted according to very general methods, regulated by the chemical nature of the compounds dealt with, and by their state of aggregation, whether solids, liquids, or gases. These methods apply also to the isolation of new compounds and the successful means is often a key to the nature of the substance.

The conditions under which a reaction will proceed are well defined for the general reactions of organic chemistry, such reactions as are typical of the more important groups, such as the alcohols, acids, aromatic hydrocarbons, etc.; modifications are occasionally required, and the influence of specific groups or substituents on the course of a general reaction is, at times, quite remarkable, but on the whole these general reactions are carried out on very similar lines. New reactions, of course, require special investiga-

<sup>1</sup> Cf. Chap. i. p. 7.

tion. This generally consists in ascertaining which of the methods employed in dealing with substances of an analogous chemical nature is the most applicable, and in a careful study of the most favourable conditions of reaction in respect to temperature, concentration, suitable solvents, the possible action of catalysers, etc. The additions to the laboratory methods of organic chemistry during the years of its most rapid development have been very few; it has been the extensive application of a somewhat limited number of methods that has accumulated the vast number of substances that are now at the disposal of the organic chemist. New methods, especially such as are applicable to amorphous, non-volatile compounds, as, for instance, the albumins, are most needed, because unless a substance can be boiled without decomposition or can be purified by recrystallisation it is at present impossible to be certain of its purity.<sup>1</sup>

It is to be borne in mind that reactions may either be constructive or destructive, or, in more precise language, synthetical or analytical. The more general laboratory preparations are synthetical, since such reactions are the more valuable aid in the study of the science, and form the most direct evidence of the structure of compounds. But syntheses of naturally occurring compounds have always been preceded by investigations of their decomposition products. These changes are of wide application and lead, according to the nature of the substance investigated, to simpler and often to known compounds, and thus give a guide to the structure of the original substance. The chemical processes which take place in the animal and vegetable kingdoms are so subtle and complex that but few of them can be imitated in the laboratory. As a consequence many organic compounds in common use can be much more readily obtained by breaking down more complicated animal and vegetable products than by synthetic means, and thus, whilst inorganic compounds are almost always obtained synthetically from naturally occurring products, the animal and vegetable kingdoms are the source of a large variety of organic compounds. It is, for instance, more practicable to prepare alcohol from sugar, obtained from plants, rather than to prepare it by

<sup>1</sup> Cf. Chap. x. p. 190.

synthetical methods in the laboratory. In the investigation of the structure of natural products special weight is attached to the recognition of certain well-defined groups by means of specific reactions.

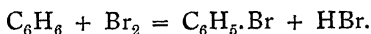
These laboratory processes will be treated consecutively in this chapter under the following heads:—

- I. *Methods for the Preparation of Organic Compounds.*
- II. *Methods for ascertaining the Chemical Nature of Organic Compounds.*
- III. *Oxidation and Reduction.*
- IV. *The application of Electrolysis to the preparation of Organic Compounds.*

In each case the methods will be illustrated by simple examples and by a description of the apparatus employed.

#### I. *Methods for the Preparation of Organic Compounds.*

*The preparation of Monobrombenzene.*—The substitution of a hydrogen atom in a hydrocarbon by chlorine or by bromine is a simple instance of a direct action between two substances. In many cases, however, this substitution only proceeds slowly and incompletely, and for the practical preparation of halogen substitution products it has been found advantageous to add small quantities of other substances which facilitate the completion of the reaction. To prepare monobrombenzene, for instance, from the hydrocarbon, a weighed quantity of benzene is placed in a flask, together with a small proportion of coarse iron filings and the proportion of bromine required by the equation:—



The flask is attached to a condenser, as shown in Fig. 12. The object of the condenser is to prevent the escape of any vapours of benzene which might be evolved at the temperature of the reaction. The attachment between a flask and condenser for such experiments as this is usually effected by means of a bored cork or rubber stopper, but since bromine attacks both these substances some other contrivance is necessary in this case. As shown in the

figure, a piece of stout rubber tubing is used, fixed outside the flask and condenser tube, so that it is scarcely exposed to the bromine vapours; another plan is to make the joint with asbestos paper or to use a ground-glass connection.

The reaction usually starts spontaneously and in order to moderate it the flask is cooled at first by placing it in a bath of ice-cold water; to complete the reaction the contents of the flask are subsequently heated over a wire gauze, as shown in Fig. 12. Fumes of hydrobromic acid are evolved, and the cessation of these fumes indicates the completion of the reaction; this evolution necessitates the

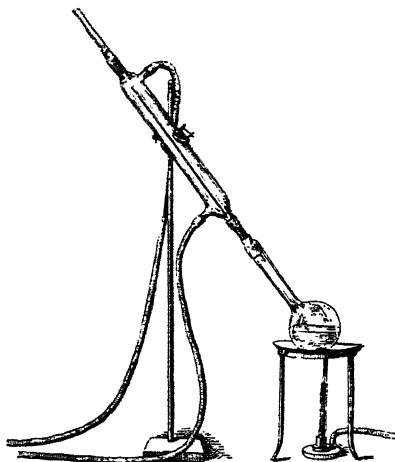


FIG. 12.

operation being conducted in a draught-place, or else a suitable absorbent for the evolved gas must be connected with the top of the condenser tube. The liberation of hydrobromic acid indicates at once that the bromine is effecting a substitution in the hydrocarbon, as expressed by the equation given above; were the hydrocarbon an unsaturated compound such as ethylene, the bromine would be simply absorbed, and no hydrobromic acid would be liberated. The reaction would, moreover, take place much more rapidly than in the bromination of a saturated hydro-

carbon. On adding bromine to an unsaturated hydrocarbon or its derivative, the absorption of the halogen is shown by its colour disappearing from the mixture as added, and the completion of the reaction by the fact that the colour of the bromine finally remains persistent. Such indications are of the greatest value in carrying out reactions of this type with new compounds, since they serve as a guide to the nature of the substances acted upon. After the completion of the reaction, the bromobenzene retains a certain amount of dissolved bromine and hydrobromic acid, together with a little unchanged benzene; in addition, a further bromination beyond the formation

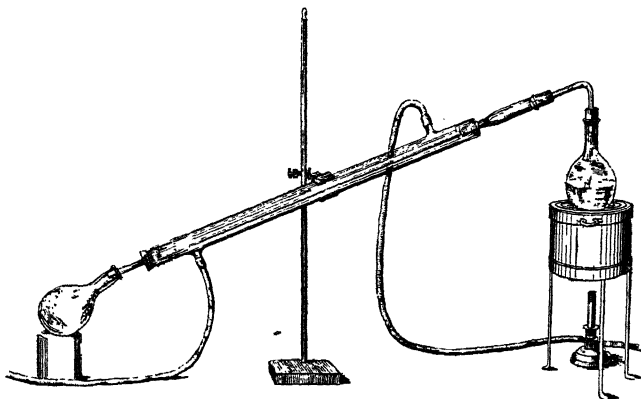


FIG. 13

of monobrombenzene is always effected to a small extent, for it is impossible to restrict the action to one single bromination product even when the quantity of bromine employed is limited to the theoretical proportion. The dibrombenzene which is formed in this case is accounted for by the fact that some of the benzene escapes bromination.

Several processes are available for isolating pure monobrombenzene from the product of the reaction. The following is a very general method of procedure:—First of all the unattacked benzene is removed by distillation. Since benzene boils at  $80^{\circ}.2$  and monobrombenzene at  $155^{\circ}$ ,



the former can be removed at the temperature of the water-bath. A cork and exit tube is, therefore, attached to the original flask and the tube connected with an

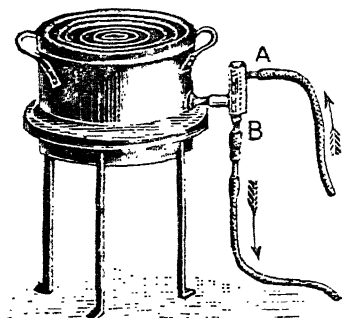


FIG. 14.

inverted condenser, as shown in Fig. 13. The water-bath is filled with water and heated to boiling, and the condensed benzene vapours are collected in the receiver at the end of the condenser tube. A constant-level water-bath is shown in Fig. 14, the advantage of which is obvious; it has an inlet tube, A, connected with the water-supply, and an outlet

tube, B, the height of which regulates the upper level of the water in the bath.

When no more benzene distils over, the contents of the flask are allowed to cool and are then transferred to a separating funnel (Fig. 15), where they are washed with dilute sodium hydroxide to remove any free bromine and hydrobromic acid that may still remain. Bromobenzene, like all haloid derivatives of the hydrocarbons, is insoluble in water, and, therefore, forms a separate layer in the separating funnel. These funnels are used for the separation of non-miscible liquids, for washing, as in the present case, and for extracting by means of a solvent. Since they are provided with a stopper at the top, as well as the one on the stem, their contents can be thoroughly shaken in order to make the washing as effective as possible; the funnel is best inverted for this purpose, a few vigorous shakings given, and the tap opened momentarily to prevent any excess of pressure remaining in the funnel. After having shaken the two liquids thoroughly together, a short time must be allowed to elapse for their separation, and then the heavier brom-

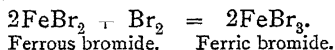


FIG. 15.

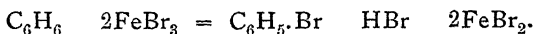
benzene is drawn off, from below, into a clean flask. The solution of alkali is poured away through the top of the funnel, and the brombenzene similarly washed with distilled water two or three times. It is then run off into a dry flask and the adhering water removed by placing a small quantity of solid calcium chloride in the flask. In all preparations in which liquids are washed with water in this manner, the product must be dried before it is fit for fractionating. The choice of the drying agent depends on the substance to be dried. Calcium chloride, potassium or sodium hydroxide, ignited potassium carbonate or fused sulphate of sodium (Glauber's salt), are most commonly employed. The drying agent must not have any chemical action on the substance to be dried; both alcohols and bases, for instance, combine with calcium chloride. The former also react with caustic alkalis, and are, therefore, dried over potassium carbonate or sodium sulphate, whilst bases, such as aniline, are dried over potassium or sodium hydroxide. The dried brombenzene should be quite clear; it is then poured off from the calcium chloride and purified by distillation, as described in Chapter VI.

This direct method of preparing halogen derivatives of the hydrocarbons is also applicable in the aliphatic group, and the practical working is quite analogous.

*Halogen Carriers.*—As stated above, the action of the bromine is greatly assisted by the presence of a little metallic iron. Aluminium bromide acts similarly, and by the aid of such substances, which act as halogen carriers, the complete bromination of benzene to the hexabrom-derivative,  $C_6Br_6$ , can be effected. The action of chlorine can be similarly assisted by the addition of a little iodine. Many such agents are made use of in the laboratory, and they all act in a somewhat similar manner. In the bromination of benzene the iron and bromine first combine to form ferrous bromide, which in presence of bromine forms the ferric salt thus:—



The latter, in presence of benzene, regenerates ferrous bromide, and the liberated bromine attacks the hydrocarbon:—



The ferrous bromide thus formed is again ready to carry a new charge of bromine to the benzene, and therefore a comparatively insignificant quantity suffices for this cycle of changes. Similarly, iodine acts as a chlorine carrier because the two elements first combine to form the unstable trichloride of iodine,  $\text{ICl}_3$ , which readily gives up two atoms of chlorine to the hydrocarbon:—



The iodine monochloride thus formed is reconverted to the trichloride by the free chlorine present, and thus a similar cycle of changes occurs.<sup>1</sup> Aluminium and cuprous salts are specially characterised by their value as carriers of certain groups; their action is not yet completely understood, but there is no doubt that they act through the formation of unstable, intermediate compounds. A group of reactions due to Friedel and Crafts, in which aluminium chloride is used, offers the most completely studied decomposition of this class.<sup>2</sup> In some of these reactions the intermediate compounds containing aluminium have been isolated.<sup>3</sup>

*Regulation of the Temperature of Reactions. The use of Solvents.*—The temperature at which a reaction should be carried out is conditioned by the mutual reactivity of the substances concerned. In the preparation of brombenzene gentle heating was necessary to complete the reaction. In other cases the two substances may react so readily, or the product of the reaction may be so unstable that the vessel in which the experiment is carried on must be cooled by ice or by a freezing-mixture of ice and salt; this is always necessary in the preparation of diazo-compounds and of azo-colours,<sup>4</sup> and even in cases where the product is quite stable it is often desirable to cool the reagents in order to avoid the formation of by-products. It is also possible to moderate a reaction by the use of solvents such as ether, alcohol, benzene, or glacial acetic acid, thus decreasing the concentration of the reacting substances; in such cases the solvent must, of course, be

<sup>1</sup> Cf. A. Sator, *J. Chem. Soc.*, 1903, lxxxiii. 729.

<sup>2</sup> Cf. B. D. Steele, *J. Chem. Soc.*, 1903, lxxxiii. 1470.

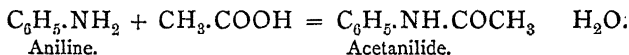
<sup>3</sup> Perrier, *Berichte*, 1900, xxxiii. 815.

<sup>4</sup> Cf. Chap. x. p. 206.

without chemical action on the substances employed or on the product or products of the reaction. When the mixture of substances requires heating, the boiling point of the mixture will of necessity limit the temperature that can be obtained in open vessels; but by employing sealed glass tubes experiments can be conducted up to 300° with safety. In working on a larger scale, autoclaves are used in place of sealed glass tubes. In reactions involving the use of solids, solvents are generally necessary, unless the temperature employed is above the melting point of the substance used, or unless, when in studying the action of a liquid on a solid, the former itself acts as a solvent for the latter.

In order to regulate the temperature at which a reaction is carried out it is necessary to heat the flask containing the reagents in a bath of some kind, even if the reaction be started with a liquid of constant boiling point. For instance, in the chlorination of toluene<sup>1</sup> it will not do to keep the liquid at its boiling point during the reaction, for as the chlorination proceeds the boiling point of the liquid rises; toluene boils at 111°, a suitable temperature for the chlorination, but the boiling point of benzyl chloride, the product of the reaction, is 176°. For temperatures below 100° a water-bath suffices; above that an oil-bath, filled with boiled linseed oil or rape oil, is generally used. Baths charged with substances of constant boiling point, such as saturated salt solutions, are also occasionally employed. The use of solvents also allows of the temperature being regulated, since they are usually so largely in excess of the reacting substances that the boiling point of the mixture is practically that of the solvent.

*The Preparation and Isolation of Solids; the preparation of Acetanilide.*—In the preparation of solid compounds the laboratory methods differ from those described only in respect to the isolation and purification of the resulting product. The preparation of acetanilide (antifebrine), from aniline and glacial acetic acid, is a simple example of the method adopted. The reaction involved is represented by the equation:—



<sup>1</sup> Cf. Chap. viii. p. 127.

To carry out the reaction, aniline is heated with an excess of glacial acetic acid in a flask connected with an upright tube or air-condenser about a yard long; the tube serves to condense the vapours of acid and aniline as they are given off from the mixture in the flask on heating, and as neither of the constituents is very volatile, and the temperature employed is only sufficient to keep the liquid simmering, it is unnecessary to use a water-cooled condenser. This simple arrangement is shown in Fig. 16.

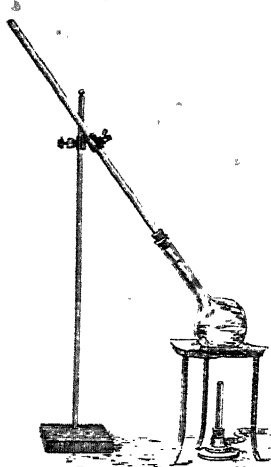


FIG 16

The reaction is completed when no more free aniline remains; this takes about twelve hours. On cooling, the whole sets to a solid mass. To purify the product it is dissolved in boiling water and the solution filtered and allowed to cool, when characteristic, tabular crystals of acetanilide separate out. These are filtered off, dried, and purified by recrystallisation from water or from dilute alcohol; it is sometimes necessary to add a little animal charcoal to absorb traces of colouring matter.

*Crystallisation.*—The first process involved after the completion of the reaction is the solution of the acetanilide in water. From a general standpoint the object of solution is, on the one hand, to remove impurities insoluble in the selected solvent, and, on the other, to separate the dissolved product from more or less soluble impurities, either by simply allowing the solution to cool or by concentration. The choice of solvent depends, of course, on the substance to be dissolved; water, alcohol, ether, benzene, light petroleum (petroleum ether), glacial acetic acid, or mixtures of these, are most commonly employed. In the case of new compounds the selection must be determined by direct experiment; the most favourable condition is when the substance shows sufficient

difference of solubility in the hot and cold solution of the solvent to allow of its separation from the former on cooling. Such separation is seldom complete, and subsequent concentration is necessary for the recovery of the whole of the dissolved product; or occasionally, the addition of a second solvent, in which the substance is sparingly

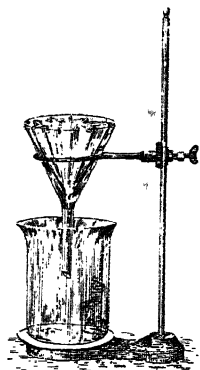


FIG. 17

soluble or insoluble, to the solution, will effect its separation in a crystalline form. The solution is effected in a flask, which in the case of inflammable solvents such as alcohol or ether must be attached to an upright condenser, the minimum quantity of solvent necessary for complete solution being employed. When the bulk of the substance is dissolved the solution is filtered through a funnel fitted with a folded filter paper (Fig. 17), and the filtrate collected in a beaker or crystallising dish. It often happens that the dissolved substance, especially if sparingly soluble, separates from the solution during the filtration and thus

clogs the space between the funnel and the filter paper. This is obviated by keeping the funnel warm, and of the many contrivances for this purpose a copper coil heated by steam, and into which the funnel fits, is the best. Fig. 18 represents this arrangement; a very gentle current of steam is sufficient.

The dissolved acetanilide separates from the solution on cooling, more or less completely, according to the quantity of solvent employed; the crystals are next filtered off, and a second crop can be obtained by the concentration of the filtrate.

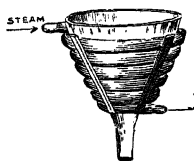


FIG 18

*Filtration.*—The form of filter very generally employed for collecting solid products is a porcelain funnel provided with a false bottom which is perforated with a number of fine holes (Fig. 19); a piece of filter paper is fitted over the holes and moistened with the solvent employed so as to

ensure its close adherence to the base of the funnel. To facilitate the filtration the funnel is fitted into the neck of a filter flask by means of a rubber stopper, and the flask exhausted by a filter-pump to which it is attached by a piece of thick-walled rubber tubing. This arrangement is shown in Fig. 20; with a good pressure of water the crystals can be almost completely dried by means of the pump. Before removing them from the filter it is necessary to wash them with a little of the solvent originally used in order to remove the adhering mother-liquor, and it is advantageous, for the sake of the subsequent

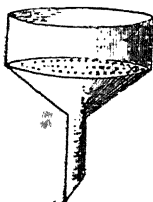


FIG. 19.

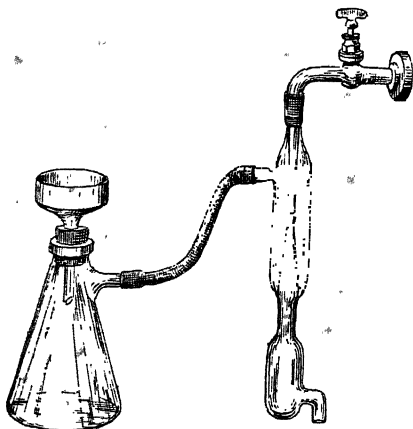


FIG. 20.

drying, to follow this washing with a further washing with a small quantity of a more volatile liquid, such as alcohol or ether, provided, of course, that the substance is not too soluble therein, and that the original solvent is miscible with that subsequently employed.

*Drying.*—The washed acetanilide, after being dried as completely as possible on the pump, is pressed between folds of filter-paper, and then transferred to a suitable dish or watch glass and the drying completed on the water-bath. In the case of substances that melt below  $100^{\circ}$  this final drying can be effected either by placing the crystals on

several folds or pieces of filter-paper with an inverted funnel over them and allowing the last traces of the solvent to evaporate spontaneously, or by putting the product in an exsiccator (Fig. 21), which can be evacuated of air by means of the filter-pump. The drying material placed in the exsiccator (calcium chloride, sulphuric acid, or potassium hydroxide) is chosen according to the nature of the substance to be dried and of the solvent to be absorbed.

The purity of the acetanilide can finally be ascertained by the determination of its melting point.<sup>1</sup> If it be impure, further recrystallisation is necessary.

The separation of two or more solid substances from one another is often effected by taking advantage of their different solubilities in a suitable solvent. This process is known as *fractional crystallisation*. It is often a long and tedious process before each constituent can be separated in a sufficient state of purity, either for identification or for analysis. The homogeneity of the separated crystals is a most useful guide as to whether the process employed is really effecting a separation of the mixed products; the purity of each product is best judged by the constancy of the melting point after recrystallisation.

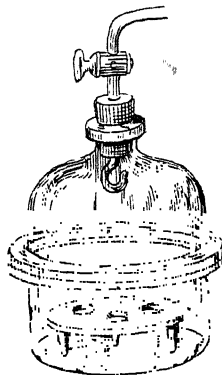


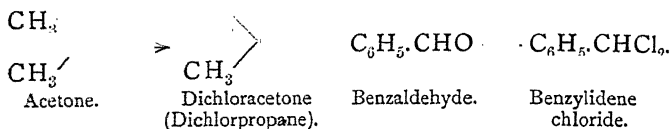
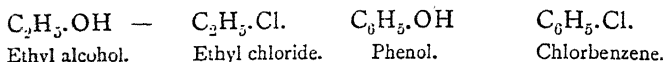
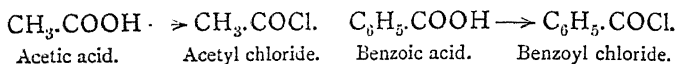
FIG. 21.

*Reactions with the chlorides of Phosphorus; the preparation of Acetyl chloride.*—The reaction of phosphorus pentachloride with alcohols, acids, aldehydes, and ketones has already been studied in reference to its bearing on the structure of these compounds.<sup>2</sup> The experimental methods adopted for carrying out these and allied reactions constitute an important and very general laboratory process. The replacement of an hydroxyl group by an atom of chlorine, or of an oxygen atom by two atoms of chlorine, which is effected by this reaction, leads to the preparation

<sup>1</sup> Chap. v. p. 82.<sup>2</sup> Chap. viii. p. 133.

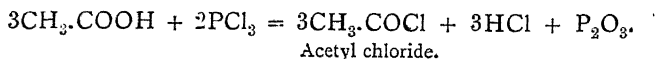
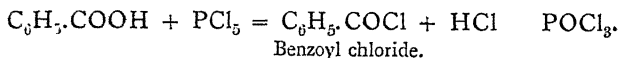


of acid chlorides and of halogen derivatives of the hydrocarbons, as illustrated in the following examples:—



The three chlorides of phosphorus, the pentachloride,  $\text{PCl}_5$ , the trichloride,  $\text{PCl}_3$ , and the oxychloride,  $\text{POCl}_3$ , are all available for effecting this substitution. They differ in their reactivity, in the products of their decomposition, and in the quantitative relations of the reactions involved. The pentachloride is the most reactive of the three, the oxychloride the least reactive. The first is, therefore, usually employed when the substance to be acted upon is attacked with comparative difficulty, whilst the latter and the trichloride are used with compounds that are more readily attacked; since, however, both the trichloride and the oxychloride are liquids with fair solvent powers, they are occasionally advantageously employed in preference to the more reactive, solid pentachloride on account of the more intimate mixture of the reacting substances that is thus possible.

Benzoyl chloride, for instance, is prepared by the action of the pentachloride upon benzoic acid, whilst the trichloride is used in the preparation of acetyl chloride. The following equations represent these decompositions:—



In the preparation of benzoyl chloride, it will be noted that one molecule of phosphorus pentachloride yields one

molecule of the acid chloride, against the three molecules of acetyl chloride which are formed by the use of two molecules of the trichloride of phosphorus. Also, that in the former case phosphorus oxychloride, a volatile compound boiling at  $110^{\circ}$ , is formed, whilst in the latter, non-volatile phosphorous oxide results. In both reactions there is an evolution of hydrochloric acid gas, which in the case of a new compound indicates that the reaction is proceeding on the normal lines, and serves further to show whether the reaction should be assisted by heat or moderated by cooling; as in the preparation of bromben-

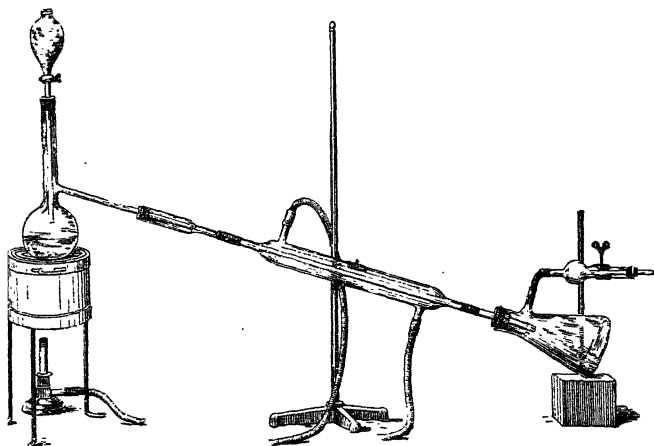


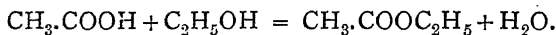
FIG. 22.

zene, this evolution of gas gradually slackens towards the completion of the reaction, and ceases when it is finished. Since the chlorides of phosphorus and also the chlorides of the organic acids are attacked by water, it is necessary to exclude all moisture in carrying out these reactions.

For the preparation of acetyl chloride, glacial acetic acid is placed in a fractionating flask, which is fitted with a cork and tap-funnel, and attached to a condenser and receiver, as shown in Fig. 22. A small tube, filled with calcium chloride, is attached to the receiver to prevent

the access of any moisture from the air, and all parts of the apparatus are very carefully dried before starting the experiment. The proportion of phosphorus trichloride indicated by the equation given above is placed in the tap-funnel and added gradually to the acetic acid in the flask, the mixture being kept cool by the water in the water-bath, in which the flask is placed. After the whole of the chloride of phosphorus has been added the water-bath is gently heated, and the heating continued until the evolution of hydrochloric acid gas, which is quite violent at first, has almost stopped. The acetyl chloride, which is a volatile liquid boiling at  $51^{\circ}$ , can then be boiled off from the phosphorous oxide, and by redistillation in a similar apparatus, in which a thermometer is substituted for the tap-funnel, it can be purified by fractional distillation. The whole operation must, of course, be conducted in a draught cupboard.

*The preparation of Ethereal Salts; Ethyl Acetate.*—Ethereal salts, such as ethyl acetate, result by the interaction of an acid and an alcohol according to the equation:—

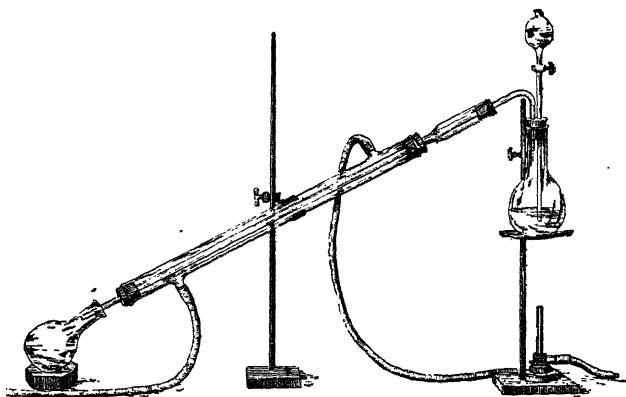


The action is reversible owing to the water that is eliminated in the decomposition; as already pointed out it reaches a limit, and therefore, for the laboratory preparation of ethereal salts the addition of a suitable dehydrating agent is a necessity. Concentrated sulphuric acid or dry hydrochloric acid gas is usually employed.<sup>1</sup>

For the preparation of ethyl acetate equal volumes of ethyl alcohol and of concentrated sulphuric acid are placed in a flask provided with a tap-funnel, thermometer, and exit tube, the latter being attached to a condenser, as shown in Fig. 23. (The thermometer is not shown.) The contents of the flask are heated to  $140^{\circ}$ , either in an oil-bath, or over a sand-bath or a piece of wire gauze, and when this temperature has been reached a mixture of equal volumes of glacial acetic acid and ethyl alcohol is added gradually through the tap-funnel. Since ethyl acetate is a liquid boiling at  $78^{\circ}$ , it distils over and is

<sup>1</sup> Chap. ix. p. 168.

condensed in the condenser; it is thus removed from the sphere of action as formed, so that there is practically no reversal of the reaction. The distillate of crude ethyl acetate is freed from acetic acid by washing with dilute sodium carbonate solution, and then from alcohol by washing with a saturated solution of calcium chloride, in which the latter is soluble. These washings are effected in the separating funnel; ethyl acetate is fairly soluble in water but not in salt solutions, and being lighter than water, forms the upper layer in the separating funnel. The washed product is finally dried over calcium chloride and purified by fractional distillation. It may be noted that its boiling point ( $78^{\circ}$ ) is lower than that of the acid from which it has been prepared; as a rule, the boiling point of an ester



FIG

is about  $120^{\circ}$  lower than the sum of the boiling points of its constituents. (Ethyl alcohol boils at  $78^{\circ}.3$ , acetic acid at  $118^{\circ}$ .) This relation is of value when an ester is expected as the product of a reaction.

When the esterification is carried out in presence of hydrochloric acid, it is usual to pass the gas, previously dried by passing through a wash-bottle containing strong sulphuric acid, into a solution of the acid in the alcohol, the ester of which is to be prepared. The necessary

apparatus is shown in Fig. 24. The hydrogen chloride is best generated by dropping sulphuric acid from a tap-funnel, A, into concentrated hydrochloric acid in a strong flask, B. The flask containing the alcoholic solution of the acid is attached to a reflux condenser. In some cases the solution is completely saturated with hydrogen chloride, but generally it is sufficient to add about 3 per cent.

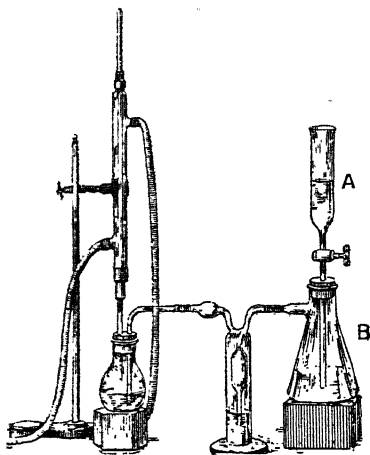
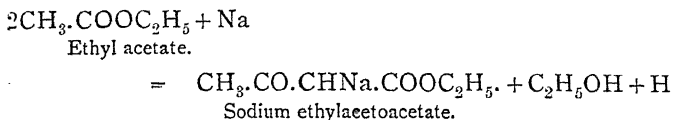


FIG. 24.

of the dry gas, and then to boil the solution for some hours.

*The preparation of Ethylacetoacetate.*—Ethyl acetate is converted into ethylacetoacetate by the action of metallic sodium or of sodium ethylate. The reaction is of wide applicability, and one which leads to many compounds of interest and importance.<sup>1</sup> The method adopted for the preparation of ethylacetoacetate is typical of many reactions in which either sodium alone or sodium dissolved in ethyl alcohol, as sodium ethylate, is employed to effect a combination between either two similar or dissimilar molecules.

The relative quantities of the reagents necessary for the experiment are represented by the equation:—



As already explained an intermediate compound takes part in the change, and the resulting sodium derivative has the alternative structure to that given above.<sup>1</sup>

Purified and dried ethyl acetate is treated with metallic sodium for the preparation. Whenever the metal is employed in experiments of this kind it is a great advantage to have it in a finely divided form, either cut up into small pieces or pressed into wire. The cut or pressed sodium must be kept under some liquid to preserve it from contact with air, and the liquid must, of course, have no chemical action upon the metal. Hydrocarbons such as petroleum—ether or benzene will serve this purpose, but anhydrous ether is usually employed. In order to obtain ether dry and free from alcohol, it is dried over calcium chloride, and then over sodium, being subsequently distilled from the latter. For the preparation the sodium is first weighed, then cut up, or pressed into wire, and kept in the anhydrous ether ready for use. For one atom-equivalent of the metal (23 grams) somewhat more than two molecule-equivalents of ethyl acetate (250 grams) are used, in accordance with the equation given above. The sodium is removed from the anhydrous ether, dried between folds of filter paper, and quickly introduced into a dry flask attached to an upright condenser. The ethyl acetate is then poured down the condenser tube into the flask, when the reaction starts at once, the heat generated being sufficient to keep the ester boiling for a time. The reaction is completed by heating the flask on the water-bath for a few hours. The sodium passes completely into solution as a salt of ethyl-acetoacetate. The separation of the free ester from its salts is effected by the addition of an acid. All organic salts are decomposed by mineral acids, such as hydrochloric or sulphuric, and these acids are commonly

<sup>1</sup> Cf, Chap. viii, p. 186.

employed to liberate such organic acids as acetic or benzoic from their salts, but they are not applicable in the case of the sodium salt of ethylacetoacetate, because they would decompose the liberated ester.<sup>1</sup> Dilute acetic acid is therefore used, the product of the reaction being treated with the acid until the salt is completely decomposed; this stage is indicated by the solution becoming acid, and is tested for with litmus paper (the ester itself has weak acid properties, but is scarcely strong enough to affect litmus paper). The products in this acid solution consist of the ethylacetoacetate, unchanged ethyl acetate, and sodium acetate formed by the neutralisation of the original salt. The two former can be separated from this solution in the separating funnel after the addition of a saturated solution of brine, which decreases their solubility in water, and then all that remains is to separate the unchanged ethyl acetate from the ethylacetoacetate. This is readily effected by fractional distillation; the ethyl acetate distils over first. Ethylacetoacetate is decomposed upon distillation at the ordinary pressure, and must consequently be distilled under reduced pressure. The details of this method have already been described.<sup>2</sup> The purified product is a liquid with a pleasant ethereal smell, boiling at 79° under 18 mm. pressure.

*The use of Metallic Compounds in the Synthetical preparation of Organic Compounds.*—Apart from the metallic salts of organic acids, a number of organic compounds are known which contain metals directly attached to alkyl radicals. These “organo-metallic” compounds, which were investigated by Frankland in the middle of last century, played an important part in building up the theory of valency; more recently they have been found to be of great value for the synthetical preparation of organic compounds. The alkyl derivatives of zinc and of magnesium are the most important for this purpose; the former were prepared and investigated by Frankland (1849), whilst the applications of the latter have only been studied during the past few years. The use of carbides, such as calcium carbide, for the production of hydrocarbons has already been dealt with.<sup>3</sup>

*Zinc Compounds.*—The organic derivatives of zinc, such

<sup>1</sup> Cf. Chap. ix. p. 180.

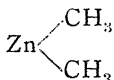
<sup>2</sup> Chap. vi. p. 1

Chap. iv. p. 51.

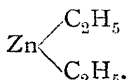
as zinc methyl and zinc ethyl, correspond to the chloride of the metal in which the halogen is replaced by an alkyl group, *e.g.*:—



Zinc chloride.



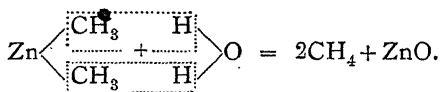
Zinc methyl.



Zinc ethyl.

They are obtained by the action of metallic zinc upon the alkyl iodides, such as ethyl iodide, and form volatile liquids which are spontaneously inflammable in air; for this reason they must be prepared and kept in an atmosphere of an indifferent gas, such as carbon dioxide, and this same precaution is, of course, necessary in making use of them for the synthesis of other compounds. Their preparation and application is accordingly somewhat difficult, and for laboratory work they have now been replaced by the more easily manipulated organic compounds of magnesium. A few of the simpler syntheses that have been effected by means of the alkyl compounds of zinc may, however, be referred to, as illustrating the character of their decompositions. They are very reactive compounds, and serve for the preparation of a great variety of hydrocarbons, alcohols, and ketones; in these syntheses one or both of the alkyl groups is introduced into the compound formed, whereby a knowledge of the structure of the latter is obtained.

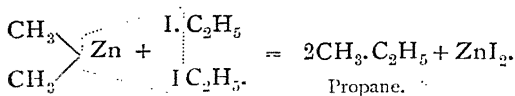
For instance, when treated with water they are decomposed at once with the formation of hydrocarbons; thus, zinc methyl and zinc ethyl give methane and ethane respectively:—



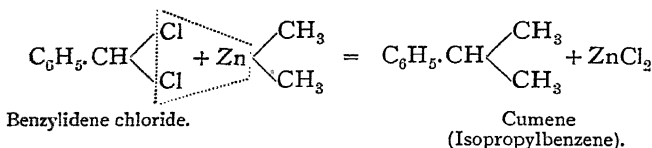
Halogen compounds are similarly decomposed with the formation of higher hydrocarbons; zinc methyl and ethyl iodide, for example, yield propane, thus proving that this hydrocarbon is methyl ethane<sup>1</sup>:—

<sup>1</sup> Cf. Chap. iii. p. 26.

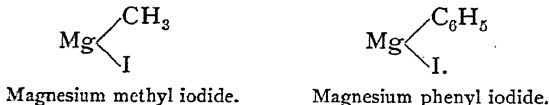




An interesting application of this reaction is the synthesis of the benzenoid hydrocarbon, cumene (isopropylbenzene), from zinc methyl and benzylidene chloride. Cumene is closely related to cymene (methyl-isopropylbenzene), the mother hydrocarbon of the terpenes,<sup>1</sup> and the proof of its structure obtained by this synthesis formed an important step in the determination of the constitution of these natural products. The main point to be decided was whether cumene contained a propyl or an isopropyl group; this synthesis proved the presence of the latter, as shown in the following equation:—



*Magnesium Compounds.*—By the action of magnesium on methyl iodide, or on iodobenzene, and other similar halogen derivatives of both aliphatic and cyclic hydrocarbons, compounds such as magnesium methyl iodide and magnesium phenyl iodide are obtained, which are characterised as being extremely reactive and readily soluble in ether:—



This solubility and the ease with which they can be prepared has rendered these alkyl and aryl magnesium derivatives specially applicable for the synthetical preparation of organic compounds, and since their discovery

<sup>1</sup> Cf. Chap. vii. p. 120.

by Grignard in 1900 they have been successfully employed in the synthesis and investigation of quite an extraordinary number of substances. The reactions occur most readily in presence of ether<sup>o</sup> and certain other solvents, which appear to form definite compounds with the organic magnesium compounds; in the case of magnesium methyl iodide, for instance, the compound with ether most probably contains a quadrivalent oxygen atom, to which the two alkyl radicals of the ether, as well as the magnesium alkyl iodide, are attached. Such compounds are called *oxonium compounds*<sup>1</sup> from their structural analogy to ammonium salts.



Diethyl oxonium magnesium methyl iodide.

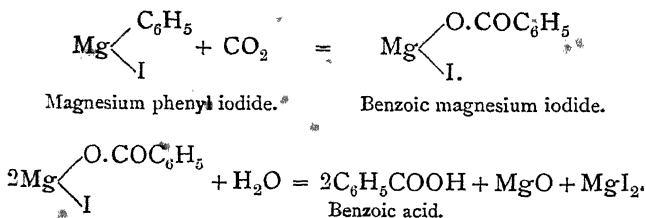
The alkyl compounds of magnesium have been largely used for the synthetical preparation of hydrocarbons, alcohols, phenols, aldehydes, ketones, and acids; they also serve for the differentiation of amines and for the recognition of the hydroxyl group.<sup>2</sup> As in the case of the zinc alkyl compounds, the syntheses thus effected are of direct value for deciding the structure of the resulting compounds. The preparation of benzoic acid from iodobenzene furnishes a typical example of the laboratory method adopted for carrying out the Grignard reaction.

*The preparation of Benzoic acid by the Grignard Reaction.*—The necessary quantity of magnesium ribbon, previously cleaned by rubbing with emery paper and cut into short lengths, is placed in a flask connected with an upright condenser (Fig. 12, p. 234), and a mixture of iodobenzene and carefully dried ether added; a small crystal of iodine is added to facilitate the reaction. It is essential to have the ether perfectly dry, as otherwise the magnesium alkyl iodide would be decomposed with the formation of benzene,

<sup>1</sup> Cf. Chap. x. p. 203.

<sup>2</sup> Cf. "The Grignard Reaction," a monograph by A. McKenzie. *British Association Reports*, 1907, p. 273.

on similar lines to the production of ethane from zinc ethyl; the removal of the contained water is effected as described under the preparation of ethylacetoacetate (p. 249). The mixture is gently warmed on the water-bath until the ether begins to boil; at this temperature the magnesium soon begins to act on the iodobenzene, and the heat evolved in the reaction is sufficient to keep the ether boiling, so that the flask is removed from the water-bath at this stage to prevent the liquid from boiling too vigorously. When the reaction slackens, a little further heating is necessary to complete the formation of the magnesium phenyl iodide, which remains dissolved in the ether. The ethereal solution thus obtained is then ready for the specific decomposition required. For the preparation of benzoic acid the flask is placed in ice-cold water, and a current of carbon dioxide, generated from a Kipp generator (Fig. 27, p. 268) and dried by washing with concentrated sulphuric acid, is passed into the solution; it is necessary to keep the temperature low, so as to prevent the volatisation of the ether. The solution gradually separates into two layers as the reaction proceeds, owing to the formation of a magnesium derivative of benzoic acid, which is insoluble in ether. When the separation appears to be complete, the whole is acidified with dilute hydrochloric acid to liberate the benzoic acid from its magnesium compound; a precipitate of impure benzoic acid is thus obtained, which is purified by dissolving it in alkali, re-precipitating with acid and crystallising from water. The reaction takes place in two stages, as represented in the following equations; an intermediate compound, benzoic magnesium iodide, is first formed, which is decomposed on acidifying with dilute acid, yielding benzoic acid:—



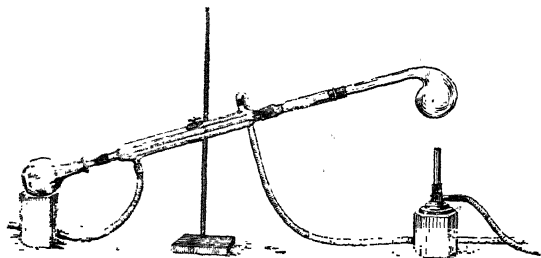
## II. *Methods for ascertaining the Chemical Nature of Organic Compounds.*

Specific qualitative reactions, such as are employed in inorganic analysis, find their equivalent in organic chemistry in the determination of the physical constants of compounds as pointed out in a previous chapter (Chap. VI.). A few specific reactions are employed for the recognition of the more commonly occurring substances, but the more important issue in the investigation of organic compounds is to ascertain their chemical nature. Aniline, for instance, gives a violet coloration with bleach solution; this is a specific test. When warmed with chloroform and alcoholic potash the formation of a compound having an extremely disagreeable smell (phenyl isocyanide) indicates the presence of aniline, but the test applies to all primary amines. This is, therefore, a test for the amino-group, but not for any individual amine. Since all organic compounds may be regarded as derived from the hydrocarbons by the replacement of hydrogen atoms by certain atoms or groups, the recognition of the latter serves as an important means for ascertaining the chemical nature of compounds. A few simple instances will suffice to indicate the method of experiment adopted.

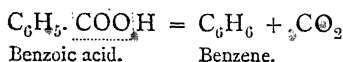
*Acids.*—The most characteristic property of acids is the formation of salts with bases.<sup>1</sup> Sodium and potassium salts are nearly always readily soluble in water, silver salts insoluble or sparingly soluble. The free acids vary greatly in solubility; the lower aliphatic acids are readily soluble, aromatic acids, such as benzoic acid, only sparingly soluble. These properties serve for the recognition of a substance as an acid. Benzoic acid, for example, though difficultly soluble in water is readily soluble in dilute alkali owing to the formation of its sodium salt, and it is reprecipitated from the alkaline solution by the addition of a mineral acid, such as hydrochloric acid. Acetic acid loses its distinctive smell on addition of alkali, and if the neutral solution be treated with silver nitrate solution a difficultly soluble silver salt is formed; from this the free acid can be liberated and identified, or the salt can be

<sup>1</sup> Cf. Chap. viii. p. 144.

dried and then ignited in a porcelain crucible, when the weight of residual metallic silver will allow of the calculation of the percentage of silver in the salt, and thus of the identification of the original acid. The sodium and potassium salts of organic acids, although readily soluble in water, are usually insoluble in ether, benzene, chloroform, and similar solvents, and advantage is taken of this in extracting acids from solutions or in separating them from other compounds. If, for instance, such a solution be made alkaline with sodium hydroxide, and then extracted with ether in a separating funnel, the sodium salt of the acid will remain in the alkaline solution, whilst other compounds present, such as bases or hydrocarbons, will be dissolved by the ether and thus separated. On acidifying, the residual alkaline solution the free acid will be liberated, and can then be extracted with a suitable solvent, or, if it be a sparingly soluble solid, it can be filtered off.



When distilled with lime or with soda-lime (a mixture of equal parts of sodium hydroxide and powdered lime), acids lose the carboxyl group and form the corresponding mother hydrocarbon, the liberated carbon dioxide being held back as carbonate by the soda-lime.<sup>1</sup> Thus, benzoic acid forms benzene, according to the equation:—

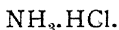


If other substituents, in addition to carboxyl, are present in the compound, these are, as a rule, unaffected by the

<sup>1</sup> Cf. Chap. viii. p. 134.

reaction, and substituted hydrocarbons result. The reaction is accordingly of value in studying the genetic relations of acids and in questions of orientation. To carry it out experimentally, the acid is mixed with about four times its weight of soda-lime and heated in a hard-glass retort over the free flame; the retort is attached to a condenser, as shown in Fig. 25, if the hydrocarbon or other decomposition product be a liquid, or if a gas, to a suitable gas-collecting apparatus. The distillation product can then be isolated by extraction with ether and subsequent fractionation, after washing and drying the ethereal solution and distilling off the solvent on the water-bath.

*Bases.*—The formation of salts with acids is the most characteristic property of bases.<sup>1</sup> If a few drops of aniline are placed in a test tube and shaken up with water, a little of the aniline dissolves, but the greater portion remains suspended in the form of oily drops. On the addition of hydrochloric acid the oil disappears and a homogeneous liquid results, owing to the formation of aniline hydrochloride which, like ammonium chloride, is readily soluble in water:—



Ammonium chloride.



Aniline hydrochloride or Phenyl ammonium chloride.

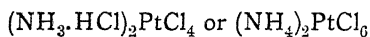
On the addition of alkali to the solution of the hydrochloride the aniline is precipitated out again as an oil, and from this alkaline solution it can be easily extracted with ether. The salts of bases, like those of acids, are insoluble in ether and similar solvents, and bases can thus be held back by acids, just as acids are by bases. In this way, they can be separated from acids as well as from neutral compounds, such as hydrocarbons, esters, ketones, etc. For instance, to separate a mixture of aniline, phenol, and benzyl alcohol, the most suitable procedure would be to dissolve the mixture in ether and shake with dilute hydrochloric acid, which would convert the aniline to its hydrochloride. The aniline could be recovered by separating the two liquids and adding alkali to the aqueous solution. The ethereal solution should then be

<sup>1</sup> *Cf.* Chap. x. p. 200.

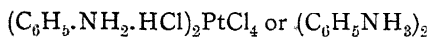
shaken with sodium hydroxide solution, which would extract the phenol in the form of its sodium salt. On separating and acidifying the aqueous solution the phenol would be recovered. The benzyl alcohol would remain in the ethereal solution and could be isolated by evaporating off the ether.

The hydrochlorides of bases are usually readily soluble in water; sparingly soluble salts are preferable for the isolation of a base, especially if the quantity be small, after the basic nature of the compound has been indicated by such tests as the above. The salts formed with chloroplatinic acid are nearly always sparingly soluble, and have the advantage that they can be readily analysed, since upon ignition a residue of metallic platinum is left. The percentage of this metal in the salt can thus be ascertained. To obtain these salts, the base is dissolved in a few drops of hydrochloric acid and a clear solution of chloroplatinic acid (platinum chloride) added. The chloroplatinates generally separate at once in a crystalline form and can be purified by recrystallisation; they vary in colour from pale yellow to orange. Their composition is analogous to that of the ammonium chloroplatinate:—

Chloroplatinic acid.

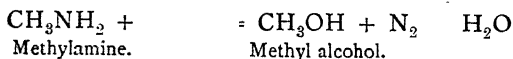


Ammonium chloroplatinate.

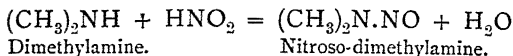


Aniline or Phenyl-ammonium chloroplatinate.

In the study of basic compounds it is important to differentiate between primary, secondary, and tertiary amines—*i.e.*, those containing the  $\text{NH}_2$  radical, the  $\text{NH}$  radical, and a nitrogen atom to which no replaceable hydrogen is attached, respectively. Several methods are available for this purpose, of which the simplest is to allow the amine to react with nitrous acid, by adding sodium nitrite to a solution of the amine in hydrochloric acid. Primary aliphatic amines react readily with nitrous acid, evolving nitrogen and forming alcohols according to the equation:—

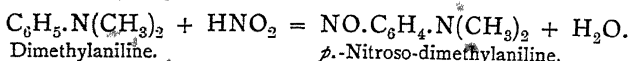


Secondary amines form nitroso-compounds, thus:—



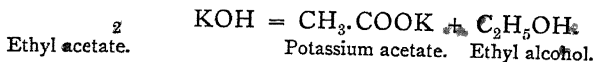
The products thus obtained can be easily distinguished and identified by their chemical and physical properties. Tertiary aliphatic amines are unacted upon by nitrous acid.

In the aromatic series the reactions are somewhat different. Primary aromatic amines give rise to diazo-compounds at low temperatures, and these give nitrogen and phenols on warming, as previously described.<sup>1</sup> The diazo-compounds can be readily recognised by their conversion into various azo-colours, and the phenols ultimately formed can also be easily identified. Secondary aromatic amines give nitroso-compounds like the corresponding aliphatic compounds. Some tertiary aromatic amines differ from the tertiary aliphatic amines in their behaviour towards nitrous acid; they give intensely coloured nitroso-compounds, in which the nitroso-group is attached to the benzene ring, *e.g.*:—



Further, all primary and secondary amines react with acetyl chloride to form acetyl derivatives, such as acetanilide, which can be readily purified, as described above (p. 239), and identified by their melting point; tertiary amines, on the other hand, are unacted on. Numerous other reactions are characteristic of bases, and serve to distinguish the different classes from one another.

**Ethereal Salts.**—Ethereal salts, such as ethyl acetate, are compounds formed, as already stated, from an acid and an alcohol, and these constituents are regenerated on saponification.<sup>2</sup> This decomposition is a ready means for recognising the chemical nature of such a substance; in the case of ethyl acetate the following equation represents the change:—



<sup>1</sup> Cf. Chap. x. p. 206.

Cf. Chap. ix. p. 169.

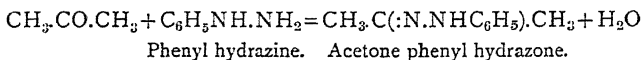
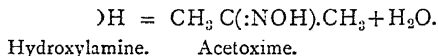


The alcohol is liberated, whilst the acid remains combined as a potassium salt. To effect the decomposition the ester is heated in a flask, attached to an upright condenser (Fig. 12, p. 234), with an excess of potassium hydroxide for an hour or two; the condenser is then reversed (Fig. 13, p. 235) and the alcohol distilled off, either from the water-bath or over the free flame, according to its volatility. It is often convenient to separate the alcohol in the distillate, from the water, by adding solid potassium carbonate. To liberate the acid from the salt that remains behind after the distillation, a mineral acid must be added, as explained above; the organic acid can then be distilled off, if volatile, or, if not, separated by other suitable means. Most esters are liquids, insoluble as a rule in water and volatile without decomposition; in addition, they have generally a pleasant ethereal smell. Such properties indicate the possibility of a compound being an ester, but these characteristics are common to many other compounds. The saponification of the compound is, on the other hand, a satisfactory proof of the chemical nature of the substance, provided, of course, the products of decomposition prove to be an alcohol and acid. The identification of these compounds will establish the structure of the ester; if they are new compounds, they in their turn must be further investigated—the acid converted into its hydrocarbon, say, and the alcohol, by oxidation, into its acid.

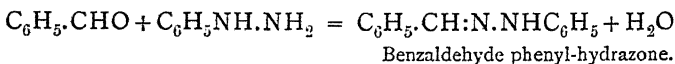
*Aldehydes and Ketones.*—The carbonyl group, CO, which is the characteristic radical of both aldehydes and ketones,<sup>1</sup> gives many well-defined reactions which are of value for their recognition and identification. When admixed with other organic compounds, aldehydes and the simpler ketones can frequently be extracted and isolated by the aid of the compounds they form with acid sodium sulphite. These compounds are soluble in water, and by shaking the mixture with a solution of acid sodium sulphite the aldehydes and ketones pass into the aqueous solution, and can thus be separated from the other constituents of the mixture; to recover them, the solution is neutralised with alkali and the carbonyl compound removed by distillation or extraction.

<sup>1</sup> Cf. Chap. viii. p. 129.

The most typical reactions of the carbonyl compounds are the formation of oximes and phenyl-hydrazones. Acetone, for instance, acts as follows towards hydroxylamine and phenyl hydrazine respectively:—



In practice, the latter of these reactions is generally used for the identification of aldehydes and ketones, as the resulting compounds crystallise well and are readily purified. A mixture of equal volumes of pure phenyl hydrazine and fifty per cent. acetic acid is used for the reaction. If this be brought in contact with benzaldehyde, for example, a flocculent precipitate at once appears, consisting of benzaldehyde phenyl-hydrazone:—



The compound is purified by recrystallisation, and identified by its melting point and other properties. Phenyl hydrazine has thus been of special service in the investigation of the sugars, which also contain the carbonyl group; in fact, without this reagent it would hardly have been possible to determine the structure of these compounds.<sup>1</sup>

Having ascertained the presence of the carbonyl group, the aldehydic or ketonic nature of a compound is usually determined by an examination of its oxidation products. Aldehydes readily yield carboxylic acids, which contain the same number of carbon atoms as the aldehyde, as represented by the general equation:—



Hence, owing to the ease with which they are oxidised, they readily reduce silver salts and certain other reagents. Ketones, on the other hand, are not so readily

<sup>1</sup> Cf. Chap. xiii. p. 331.

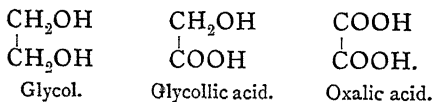
oxidised; they do not reduce the noble metals, and if subjected to the action of vigorous oxidising agents they decompose and yield carboxylic acids containing fewer carbon atoms.

Specific reactions for other groups are thoroughly worked out, and are continually applied in laboratory work. Amides, sulphonic acids, ethers, phenols, and hydrocarbons all give certain general reactions which show typical variations amongst aliphatic, as compared with cyclic compounds. Further, these general reactions are often affected by the presence of other substituting groups, and such mutual influences have always to be considered.

### III. *Oxidation and Reduction.*

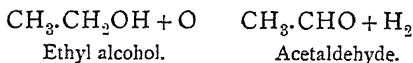
The processes of oxidation and reduction are of great practical value in the study of the mutual relations and structure of compounds; also, they have many important technical applications.

*Oxidation.*—Organic compounds, according to their nature, react very differently towards oxidising agents, and in addition, the products formed vary with the nature of the oxidising agent employed. When, for instance, the divalent alcohol, glycol, is oxidised by nitric acid, oxalic acid is one of the chief products, but with milder oxidising substances intermediate products in the oxidation, such as glycollic acid, can be isolated:—



The chief oxidising agents used are nitric acid, potassium permanganate, sodium or potassium bichromate, chromic acid, manganese peroxide and hydrogen peroxide. Alcohols, aldehydes, ketones, aromatic hydrocarbons and bases all undergo specific reactions when oxidised; the conditions of reaction and the proportion of the oxidising agent employed are regulated according to data ascertained from experiment. All primary alcohols form aldehydes

upon mild oxidation; ethyl alcohol, for example, yields acetaldehyde, according to the equation:—



This characteristic oxidation is conducted in the apparatus shown in Fig. 26. The oxidising agent used is chromic acid, but instead of employing the free acid a mixture of sodium bichromate and sulphuric acid is preferred, which allows of the better regulation of the reaction. Dilute sulphuric acid is placed in the flask A; this is heated till it just begins to boil, and then a mixture of sodium bichromate dissolved in water and alcohol, in suitable

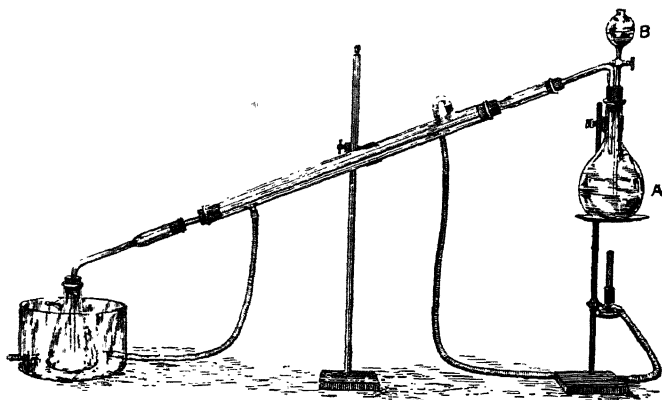
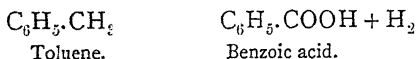


FIG. 26.

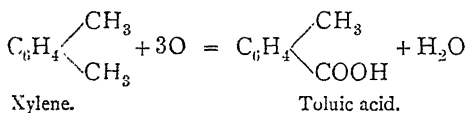
proportions, is added gradually through the tap-funnel B. It is not necessary to continue the heating during this addition, as the heat evolved in the reaction is sufficient to keep the mixture boiling; that an oxidation is effected is at once shown by the change in colour of the yellow bichromate solution to the green of a chromium salt. The bichromate is reduced, and the alcohol oxidised by the liberated oxygen. The aldehyde distils over as it is formed, together with some unchanged alcohol; since aldehyde boils at  $21^\circ$ , special cooling is required for its

condensation. The receiver attached to the condenser is, therefore, placed in a freezing-mixture of ice and salt. When all the alcohol has been added, the oxidation may be completed by further heating, and if, on the addition of more bichromate, the colour of the latter remains persistent, it is a sign that the reaction is finished. The distillate has then to be purified, and in the case of acetaldehyde it is best, on account of its low boiling point, to convert it into aldehyde-ammonia. Aldehyde-ammonia is a crystalline compound, and the aldehyde can easily be regenerated from it, and thus obtained pure.

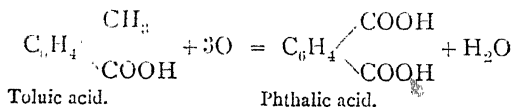
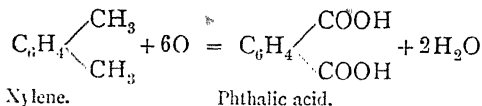
An example of a more complete oxidation is the conversion of the side chain of an aromatic hydrocarbon to the carboxylic acid group. The oxidation of toluene to benzoic acid is, for instance, represented by the equation:—



If several side chains are present, either all or a portion of them may be thus oxidised, according to the reagent used. Thus, on boiling with dilute nitric acid (a comparatively mild oxidising agent), xylene is converted to toluic acid:—



Chromic acid and potassium permanganate act more vigorously, and generally oxidise all the side chains present to carboxyl groups; both xylene and toluic acid, for instance, give the dibasic acid, phthalic acid:—



As an example of the action of potassium permanganate, the conversion of *p*.toluic acid to *p*.phthalic acid may be taken. The toluic acid is dissolved in sodium hydroxide, the solution warmed on the water-bath, and a solution of potassium permanganate gradually added. The red colour of the permanganate disappears at first, indicating that an oxidation is being effected, and the addition is continued until the colour persists in the oxidised solution, which shows that the oxidation is complete. The permanganate, which is a derivative of the highest oxide of manganese,  $Mn_2O_7$ , is itself reduced to manganese dioxide,  $MnO_2$ , which separates out as a hydrate, and must be filtered off. The alkaline filtrate containing the sodium phthalate is then acidified with hydrochloric acid, when the free phthalic acid separates out completely on cooling, and can be purified by recrystallisation.

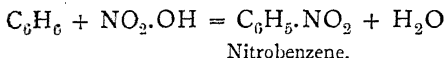
Other oxidation processes are conducted on similar lines, with such changes in the method as are necessitated by the nature of the oxidising agent employed, and of the substance oxidised. The product of oxidation is isolated by extraction, crystallisation, or other suitable process, according to its nature. In many cases more than one product can result by the oxidation, and the restriction of the reaction to the formation of one compound only is then effected, either by a suitable selection of the oxidising agent, or by specific conditions of the reaction, which must be determined by direct experiment.

*Reduction.*—Reduction processes are the reverse of oxidation processes, but many reduction products can be obtained which cannot be converted into the original compounds by direct oxidation.

Nascent hydrogen, generated from a metal such as iron, tin, or zinc, and a mineral acid, is one of the most useful reducing agents. Sodium, sodium amalgam and readily oxidisable compounds such as hydriodic acid, sulphuretted hydrogen and ferrous sulphate are also used, and in some cases hydrogen gas in presence of finely divided nickel. As in the case of oxidising agents these reagents differ in their action, especially in regard to the degree of reduction that can be effected. Acetaldehyde can be reduced to ethyl alcohol by zinc and hydrochloric acid, but to obtain ethane from the alcohol, hydriodic acid is necessary.

Unsaturated hydrocarbons and their derivatives form saturated compounds on reduction, alcohols form hydrocarbons, ketones form alcohols and other intermediate compounds, nitro-compounds and nitriles yield amines. In all these cases the reduction products give indications of the chemical nature of the original compound; in addition they include many substances of technical importance, amongst which the aromatic amines which are employed in the preparation of most of the aniline colours stand foremost. As a typical reaction of this class the preparation of aniline itself from nitrobenzene will serve to illustrate the laboratory method adopted.

The hydrocarbons obtained from coal tar are the starting point for the preparation of the amines employed in the colour industry. These are first converted into nitro-compounds by the action of nitric acid and then reduced.<sup>1</sup> The nitration of benzene takes place according to the equation:—

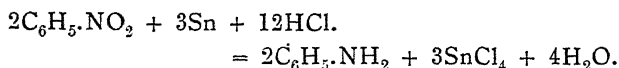


The hydroxyl group of the nitric acid unites with an atom of hydrogen from the benzene ring to form water, and although it is quite easy to effect this reaction without any dehydrating agent, it is extremely difficult to complete it, because the separated water dilutes the nitric acid, and thus inhibits the nitration. An increase of temperature favours the completion of the change, but then the nitration usually proceeds too far, with the result that di-nitro-compounds and other more highly nitrated substances result. To avoid this, and at the same time to complete the formation of the mono-nitrobenzene, a mixture of concentrated sulphuric acid and nitric acid is employed; the former absorbs the water separated, and by thus preventing the dilution of the nitric acid, allows the reaction to be regulated.

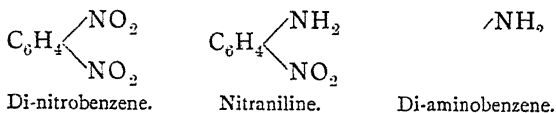
Many reducing agents are available for converting nitrobenzene into aniline. In the laboratory, tin and hydrochloric acid are used; on the large scale, iron and hydrochloric acid. The nitrobenzene is placed in a large

<sup>1</sup> Cf. Chap. x. pp. 194 and 216.

flask, together with the necessary quantity of tin, and hydrochloric acid is added gradually. A fairly violent reaction sets in, which necessitates the cooling of the flask; when the whole of the acid has been added, the reduction is completed by gently warming the contents of the flask on the water-bath. In order to liberate the aniline from the acid solution in which it is dissolved as a salt, an excess of sodium hydroxide is added and the free base distilled from the solution by means of steam. The aniline is then extracted from the distillate with ether, the ethereal solution dried over potassium hydroxide and the residue, after distilling off the ether, purified by fractional distillation. This method of procedure holds for all amines. The reduction is represented by the equation:—



This process if applied to a di-nitrobenzene,  $\text{C}_6\text{H}_4(\text{NO}_2)_2$ , would reduce the two nitro-groups at once to form a di-aminobenzene. With milder reducing agents, such as sulphuretted hydrogen in alkaline solution, the reduction can be restricted to one nitro-group and an intermediate product, nitro-aminobenzene (nitraniline), obtained:—



Quite another class of reductions is effected by distilling oxygenated compounds over red-hot zinc dust. The apparatus employed is shown in Fig. 27.

The substance to be reduced is placed at the upper end of a piece of hard-glass tubing, A, open at both ends, the rest of the tube being filled with zinc dust, which is best prepared by coating small pieces of pumice with moistened zinc dust and then drying them. The zinc dust adheres quite well to the pumice, and thus presents a large surface for the decomposition. The reduction is aided by conducting a current of dry hydrogen through the tube. This is obtained from the generator B, and is dried by strong



sulphuric acid in the wash-bottle, C. A suitable receiver is attached to the lower end of the tube. The tube, after being filled, is placed in a combustion furnace, as shown, and after the contained air has been completely removed by hydrogen, the layer of zinc dust is heated to a good red heat. The substance is next gently heated; as its vapours (it must be a compound which distils without decomposition) pass over the heated zinc, reduction takes place,

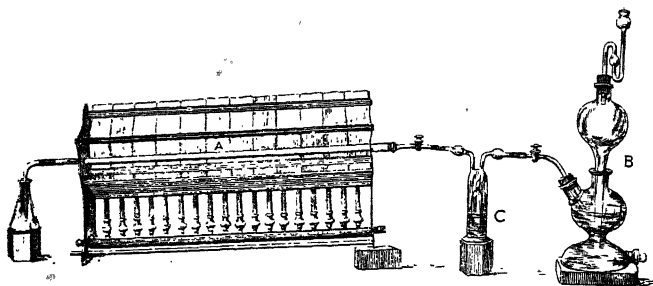
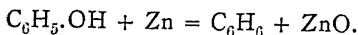


FIG. 27

and the reduced product is collected in the receiver. Phenol is, in this way, reduced to its hydrocarbon benzene, according to the equation:—



The method is important for obtaining the hydrocarbon corresponding to oxygenated compounds, especially in the aromatic group. It was thus that Graebe and Liebermann in 1868 recognised the hydrocarbon anthracene as the mother substance of alizarin, a discovery that soon led to the synthetical preparation of the latter from the hydrocarbon.<sup>1</sup>

#### IV. *The application of Electrolysis to the preparation of Organic Compounds.*

An interesting synthesis of ethane was effected by Kolbe in 1849 by passing an electric current through a solution

<sup>1</sup> Cf. Chap. xv. p. 427.

of potassium acetate, and other aliphatic hydrocarbons were subsequently prepared in an analogous manner.

With the development of the knowledge of electrolysis, methods for the electrolytic preparation of organic compounds have been considerably extended; these differ both in their character and, to some degree, in their applications from other laboratory methods, and form an important addition to the processes employed in practical organic chemistry.

*The Theory of Electrolytic Dissociation.*—Since the publication by Arrhenius in 1887 of his theory of electrolytic dissociation a great impetus has been given to the study of all problems connected with electrolysis. The theory has had a remarkable and wide-reaching influence throughout the whole domain of chemistry, and its services have been successfully applied to elucidate the most varied problems of the science, from qualitative analysis to animal and vegetable metabolism. This marked applicability has rendered the theory generally acceptable to both chemists and physicists. The special study of the subject of electrolytic dissociation falls within that branch of the science now known as "Physical chemistry"; it is quite beyond the scope of this book to consider even some of the more general applications of the theory, but an outline of its nature will be helpful before proceeding to the consideration of the electrolytic preparation of organic compounds.<sup>1</sup>

There are two classes of conductors of electricity. Metals, alloys, carbon, and a few other substances constitute the one class; these undergo no material change when electricity passes through them. They get hot during the passage of the current, and the conduction follows the same laws as that of heat. Conductors of the second class are called *electrolytes*, and consist of salts, either in solution or fused, and of solutions of bases.

<sup>1</sup> An account of modern views of electrolysis and of the theory of electrolytic dissociation will be found in the following books:—

*Electrochemistry*, R. A. Lehfeldt, 1904.

*Introduction to Physical Chemistry*, J. Walker, 4th edition, 1907.

*Theory of Solution*, W. Whetham, 1902.

*The Theory of Electrolytic Dissociation and some of its Applications*, H. C. Jones, 1900.

and acids. The conduction of the current by electrolytes is invariably accompanied by chemical decomposition, the electricity flowing with the components of the electrolyte, between two oppositely charged metallic plates or electrodes, which convey the current to the solution. When, for instance, a solution of sodium chloride is electrolysed the sodium moves from the positive part of the circuit to the negative, whilst the chlorine moves in the opposite direction. Metals generally, and hydrogen behave like sodium, and are consequently called electro-positive elements, whilst bromine, iodine, acid radicals and the hydroxyl group, which, like chlorine, move from the negative to the positive part of the circuit, are called electro-negative. On reaching the electrodes these components of the electrolyte, to which Faraday gave the name of *ions*, give up their charge and either combine to form free molecules or undergo secondary decompositions. Thus, in the electrolysis of a sodium chloride solution, the liberated chlorine ions, which are in the atomic state, combine with each other to form free chlorine,  $\text{Cl}_2$ , whilst free sodium is similarly formed, which, unless immediately removed, acts upon the water of the solution to form sodium hydroxide with the liberation of hydrogen. Complications may follow unless the initial products of electrolysis are efficiently separated, and it is such separation that is essential for the success of the manufacturing processes now in use for the preparation of chlorine and caustic soda by the electrolysis of common salt.

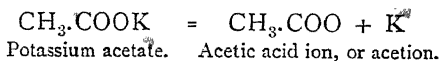
According to the Arrhenius theory of electrolytic dissociation, the electric current can only be conveyed by free ions, which in the above case are represented by free atoms of sodium and chlorine, and in the aqueous solutions of all electrolytes a greater or less proportion of the dissolved molecules are regarded as separated into their constituent ions, which exist in the solution independently of one another, and each of which is electrically charged. The passage of the electric current only gives direction to these charged ions; their separation from the original molecule occurs upon solution and is not due to work expended by the electric current, the resistance being due solely to the viscosity of the solvent, which impedes the progress of the ions towards the electrodes.

At first sight, the view that free sodium and free chlorine exist side by side in a solution of sodium chloride appears somewhat strange, especially in the light of older ideas on the nature and constitution of dissolved salts, and also because such free atoms show none of the properties usually assigned to them. The free sodium does not decompose the water of the solution, nor is there any apparent evidence of the presence of free chlorine. This absence of the usual chemical properties is attributed to the dissociated ions being electrically charged, and as long as they retain these charges their properties are entirely different to those of the free substances; if the charges are given up, as occurs when the ions reach the electrodes during electrolysis, then the elements appear with their ordinary chemical characters. The nature and origin of these charges is at present not understood.

Just as a solution of sodium chloride is regarded as containing the electro-positive ion sodium and the electro-negative ion chlorine, so are other salts looked upon as dissociated in solution into constituent ions—sodium nitrate, for instance, into the metal and the acid ion,  $\text{NO}_3$ ; sodium sulphate into sodium and the electro-negative ion,  $\text{SO}_4$ ; a base, such as sodium hydroxide, is dissociated in solution into sodium and the electro-negative radical hydroxyl, an acid, such as hydrochloric, into electro-positive hydrogen and electro-negative chlorine. This conception of the condition of dissolved salts, acids, and bases will be rendered more evident by the representations:—

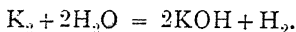


In the case of a solution of potassium acetate the constituent ions of the dissociated molecule consist of the electro-positive metal and the electro-negative acid ion, called the acetic acid ion or acetion:—

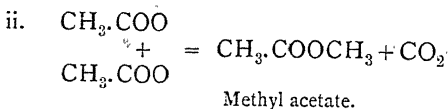
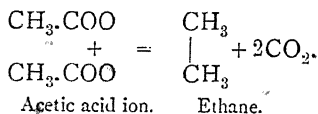


When an electric current is passed through the solution the potassium ion travels to the negative electrode, called

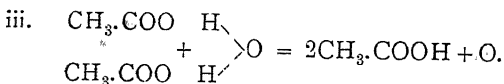
the *cathode*, where it gives up its charge, and uniting with a second potassium ion forms free potassium; this in presence of water, forms potassium hydroxide, and liberates hydrogen, the ordinary decomposition represented by the equation:—



The electro-negative ion, which travels to the opposite electrode, called the *anode*, may act either upon itself or directly upon the water of the solution. In the former case either of the following decompositions may occur:—



By reacting simply with the water of the solution, acetic acid is formed and oxygen liberated:—

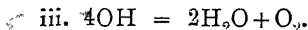
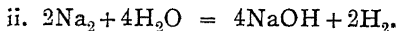
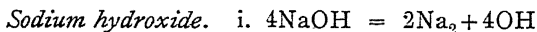
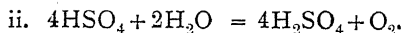
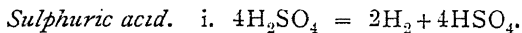


The modern conceptions of electrolysis have indicated the conditions that determine one or other of these decompositions. A dilute solution and a weak current favour the third decomposition, whilst when a concentrated solution of the acetate is used or when a strong current is employed, the first two decompositions are favoured. Either of the latter conditions will cause the acid ions to be more crowded together or concentrated, and thus give them greater opportunity of acting upon each other; a dilute solution or a weak current will, on the other hand, tend to cause a less concentrated separation of the acetic acid ions, and thus give greater opportunity for their reacting with the surrounding water. In the case of potassium or sodium acetate, ethane is the chief product formed under the conditions favourable for the first two

decompositions; in the case of salts of other organic acids the extent to which one or other of these two decompositions obtains depends upon the nature of the acid, whilst other changes, resulting in the formation of unsaturated hydrocarbons of the ethylene series, may also occur. There have been many applications of the electrolysis of salts of organic acids to the preparation of hydrocarbons, of dibasic acids,<sup>1</sup> and of aldehydes.<sup>2</sup>

With the exception of the organic acids, bases, and their salts, most organic compounds are not electrolytes either in solution or when fused; hence, direct electrolytic methods have only a limited application for the preparation of organic compounds.

The more interesting electrolytic methods of preparation are of an indirect character; they depend upon the utilisation of the hydrogen or oxygen liberated by the electrolysis of an inorganic acid or base, such as sulphuric acid or sodium hydroxide, for the reduction or oxidation of organic compounds. In the electrolysis of sulphuric acid the liberated ions are hydrogen and the sulphuric acid ion  $\text{HSO}_4$ ; the latter in presence of water liberates oxygen and forms sulphuric acid again. The ions of sodium hydroxide are sodium and the electro-negative ion, hydroxyl; in presence of water the sodium forms sodium hydroxide with liberation of hydrogen, whilst the hydroxyl ions, by their unification at the anode, liberate oxygen with the simultaneous formation of water. These changes may be represented as follows:—



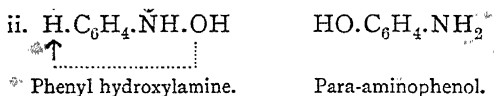
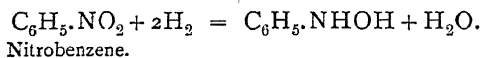
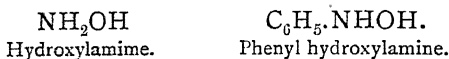
In both cases hydrogen and oxygen are liberated, whilst the original product, sulphuric acid or sodium hydroxide,

<sup>1</sup> Cf. Crum Brown and Walker, *J. Chem. Soc. Abstracts*, 1891, p. 1192; *Annalen*, cclxxiv., 1893, 41.

<sup>2</sup> Cf. Wohl and Schweitzer, *Berichte*, 1906, xxxix., 890.

is continuously regenerated in the solution. By carrying out such electrolytic decompositions under suitable conditions in presence of organic compounds, the liberated hydrogen or oxygen can be employed for their reduction or oxidation.

*The Electrolytic preparation of para-Aminophenol.*—The reduction of nitrobenzene is an instructive example of this indirect electrolysis. With ordinary chemical reducing agents, such as tin and hydrochloric acid, nitrobenzene usually yields aniline,<sup>1</sup> but when reduced by electrolytic hydrogen in sulphuric acid solution para-aminophenol  $\text{HO.C}_6\text{H}_4.\text{NH}_2$  is formed.<sup>2</sup> This change when first discovered, appeared very abnormal; it was explained by the suggestion that a phenyl derivative of hydroxylamine is first formed, which undergoes a molecular rearrangement with the formation of para-aminophenol. These changes are represented by the following equations:—



As in many other molecular rearrangements in the aromatic group, a para-compound results from the change, a hydrogen atom and a hydroxyl group changing places as indicated by the dotted lines.

At the time when this suggestion of the course of the reduction was put forward phenyl hydroxylamine was not known. It has since been prepared, and has been found to be very unstable in presence of strong sulphuric acid, being most readily changed to para-aminophenol; this confirmation of the correctness of the above explanation has been substantiated by subsequent electrolytic experi-

<sup>1</sup> Cf. this chap., p. 266.

<sup>2</sup> Gattermann, *Berichte*, 1893, xxvi. 1844.

ments, which have proved that phenyl hydroxylamine is formed during the electrolytic reduction.

The arrangement of the circuit for an electrolytic preparation such as that of aminophenol<sup>1</sup> is shown in the following diagram (Fig. 28):—

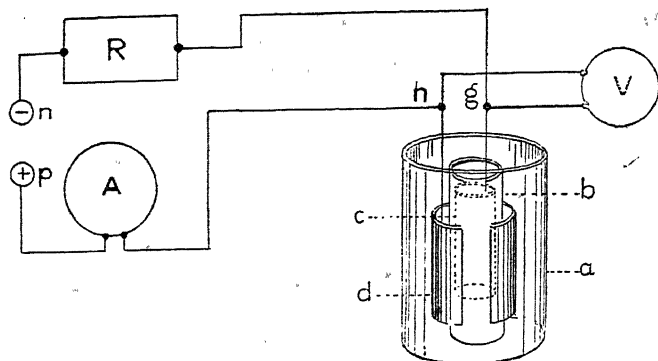


FIG. 28.

The electrolytic cell consists of a glass beaker, *a*, inside which an ordinary porous earthenware cell, *b*, is placed; both the beaker and the porous cell are provided with platinum electrodes, *c* and *d*, made of platinum foil or gauze attached to pieces of platinum wire, which latter serve for connecting to the binding screws of the circuit, *g* and *h*. The electrode in the porous cell serves as the cathode, that in the beaker as the anode; the object of the porous cell is to keep the products of decomposition in the anode and cathode compartments apart, whilst still allowing the current to pass between the two poles. The current is supplied from the terminals of the battery, *p* and *n*; the positive wire is taken through the ammeter, *A*, to the anode,

<sup>1</sup> Details of electrolytic methods for the preparation of organic compounds will be found in:—

*Electrolytic Preparations*, Elbs., trans. by Hutton, 1903.

*Practical Methods of Electro-Chemistry*, F. M. Perkin, 1905.

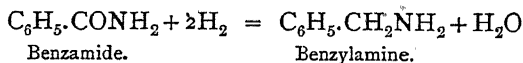
"Die Electrochemische Reduction organischer Nitrokörper," K. Brand, 1908. *Sammlung chem. u. chem.-technischer Vorträge*.



and the negative wire through the resistance,  $R$ , to the cathode. The ammeter serves for the measurement of the current and the resistance for regulating it; a voltmeter,  $V$ , is inserted in a branch of the circuit to measure the electromotive force between the electrodes of the cell. These measuring and regulating instruments are quite necessary for the success of electrolytic preparations, as the yield and, in some cases, the nature of the products formed depend upon the quantity and pressure of the electrical energy supplied. Secondary batteries are preferably used as the source of the electric current.

To carry out the preparation, a solution of nitrobenzene in concentrated sulphuric acid is placed in the porous cell, and concentrated sulphuric acid, diluted with a little water, in the beaker. The whole is warmed to about  $80^{\circ}$ , and then electrolysed at this temperature with a current of 4 to 6 ampères per 100 square centimetres of cathode surface, and an electromotive force of 7 to 8 volts. After the current has passed for a short time the contents of the inner cell begin to turn blue and to thicken, and after a while a crystalline magma of the sulphate of aminophenol separates. The decomposition is complete in from 12 to 14 hours. To separate the product of the reaction, the crystalline sulphate is filtered off, washed, purified, and then converted into the free base. If the nitrobenzene be dissolved in a mixture of dilute sulphuric acid and alcohol instead of in the concentrated acid, aniline is obtained as the chief product of the reduction. This is because phenyl hydroxylamine is more stable in presence of dilute than of strong acids, and instead of undergoing the molecular change to aminophenol, it is further reduced to aniline.

Electrolytic reduction has also been applied to the preparation of hydrides of the bases of the pyridine and quinoline groups, and with special success to the conversion of amides into amines, benzamide, for instance, being reduced to benzylamine<sup>1</sup>:—



<sup>1</sup> Tafel and Baillie, *Berichte*, 1899, xxxii. 68; Tafel, *Berichte*, 1900, xxxiii. 2209; Tafel and Stern, *Berichte*, 1907, xl. 2831.

Electrolytic oxidation processes, both in alkaline and in acid solution, have also been studied; in some few instances they have proved either more advantageous than the ordinary methods of oxidation or have led to the formation of different products,<sup>1</sup> but it is usually more difficult to stop the reaction at the right point than in the case of electrolytic reduction.

<sup>1</sup> Cf. Elbs, *J. Chem. Soc. Abstracts*, 1897, lxxii. 332. A. G. and F. M. Perkin, *J. Chem. Soc.*, 1904, lxxxv. 243; 1908, xciii. 1186. H. D. Law, *J. Chem. Soc.*, 1905, lxxxvii. 198; 1906, lxxxix. 1437.

## CHAPTER XII.

### STEREOCHEMISTRY.

The limitations to the law of the linking of atoms, as previously considered—The optical activity of organic compounds—Pasteur's investigations on the tartaric acids.

Van't Hoff and Le Bel's theory of the asymmetric carbon atom.

*The tetrahedron symbol for the carbon atom.*—The stereochemistry of the tartaric acids—Racemic combinations and their resolution into optically active compounds—The synthetical preparation of optically active compounds—Asymmetric synthesis.

*The geometrical isomerism of unsaturated compounds.*—Stereochemical considerations regarding the formation of cyclic compounds.

*Asymmetric optically active compounds of silicon, tin, sulphur, and selenium.*

*The stereochemistry of nitrogen.*—Asymmetric optically active nitrogen compounds.

THE law of the linking of atoms marked a great advance in the knowledge of the structure of compounds, especially in explaining isomeric relations previously incomprehensible, such as that of the mixed ethers.<sup>1</sup> But, as previously stated, other conditions of isomerism were observed which, although in no way opposed to the teachings of the above law, lacked explanation by its means.<sup>2</sup> These newer isomeric relations led to the study of the spatial arrangement of the atoms within the molecule, a subject to which the name *Stereochemistry* (from στερεός, solid) was given by Victor Meyer in 1890; the development of this branch of chemistry will be dealt with in the present chapter.<sup>3</sup>

<sup>1</sup> Cf. Chap. ii. p. 30.

<sup>2</sup> Chap. ii. p. 31.

<sup>3</sup> A full account of the subject is given in the following books:—

*Stereochemistry*, by A. W. Stewart, 1907.

*Lehrbuch der Stereochemie*, A. Werner, 1904.

As long ago as 1838 Biot<sup>1</sup> observed that a solution of tartaric acid, in common with several other naturally occurring organic substances, possesses the power of deflecting the plane of polarisation of a plane-polarised beam of light, but that racemic acid, which has the same composition as tartaric acid, does not possess this optical property. Both acids are dibasic, and yield very characteristic salts, amongst them sodium-ammonium salts, of the composition  $C_4H_4(Na.NH_4).O_6$ . The salt of tartaric acid was found by Mitscherlich (1844) to be optically active like the free acid, that of racemic acid to be similarly inactive, and he adds the following interesting remark in respect to the two salts:—"They have the same chemical composition, the same crystalline form with the same angles, the same specific gravity, the same double refraction, and, therefore, their optical axes form the same angle. Their aqueous solutions show the same refraction. But the dissolved tartaric acid salt rotates the plane of polarisation and the racemic salt is indifferent. . . . But the nature and number of the atoms, their arrangement, and their distance from one another is the same in both cases."

*Pasteur's investigations on the Tartaric Acids.*—Such marked analogy without identity appeared inexplicable until Pasteur (1848) pointed out certain differences in the salts of tartaric and racemic acids which had escaped the notice of previous investigators. The crystals of potassium tartrate, although of the same form and system as those of potassium racemate, were shown by Pasteur to possess certain small faces, called hemihedral faces, which were absent in the racemates. Hemihedral faces are such as occur in only half their possible number, and two opposite hemihedral forms are possible with the class of crystals to which the tartrates belong. All tartrates and tartaric acid itself show this crystallographic difference from the racemates and racemic acid. Pasteur next discovered that when a solution of sodium-ammonium racemate is allowed to evaporate at a low temperature, the crystals that separate are not homogeneous, but consist of two forms differing only in the position of the hemihedral faces. The one form was identical with the double salt derived

<sup>1</sup> *Ann. Chim. Phys.*, 1838, [2] lxi., 27.

from tartaric acid; the other had the hemihedral face on the opposite side of the crystal. This difference in crystalline form is shown in the following figures, in which the hemihedral faces are darkened:—

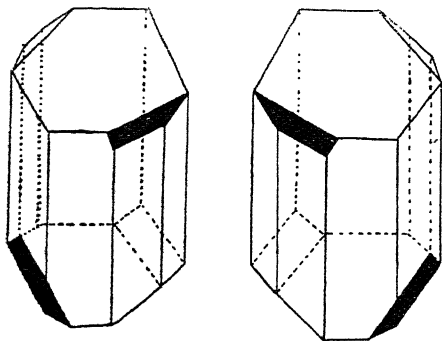


FIG. 29.

By mechanically separating the two forms of crystals Pasteur found that their aqueous solutions were both optically active, and that they rotated the plane of polarised light to the same extent, but in opposite directions. When mixed in molecular proportions, an optically inactive solution resulted. Further, Pasteur prepared the free acids from the salts; these again were optically opposite in solution, and one was identical in all respects with ordinary tartaric acid.

Crystals having oppositely developed hemihedral faces are called *enantiomorphs*; they cannot be superposed, but are related as an object to its reflection in a mirror, or as the right hand to the left, as seen in Fig. 29. Pasteur, after extending his study of the tartaric acids to other organic compounds, came to the conclusion that "optically active carbon compounds possess the property of crystallising in enantiomorphous forms." The resolution of racemic acid into the optical isomers and the recombination of the latter to form an inactive combination are typical of many similar changes which have since been studied. The term, *racemic modification*, is now generally used for the optically inactive isomer, which can be thus

decomposed, and the separated products are known as the *dextro-rotatory* and *laevo-rotatory* modifications, according as they rotate the plane of polarised light to the right or to the left. Ordinary tartaric acid is dextro-rotatory; also, its hemihedral faces are developed on the opposite side of the crystal to those of the laevo-rotatory acid. Pasteur completed his investigations on this subject by the discovery that a fourth isomer of tartaric acid is formed when the dextro-rotatory acid is heated. This new compound, which is now called *inactive* or *meso-tartaric acid*, differs from racemic acid in its physical properties, and especially in the fact that, though inactive, it cannot be split up into two oppositely active forms. There are several methods known for decomposing inactive combinations, but none of them have availed in the case of meso-tartaric acid; nor are they likely to, for, as will be seen, this inactivity is constitutionally different from that of racemic acid.

Very many other naturally occurring substances are known which, like ordinary (dextro-rotatory) tartaric acid, can deflect the plane of polarised light when dissolved in water, whilst amongst inorganic compounds this property is restricted to crystalline solids, such as quartz, sodium chlorate, and sodium periodate. Both dextro-rotatory and laevo-rotatory crystals of sodium chlorate, for instance, are known, but when dissolved in water the solutions are inactive and in every respect identical. This fundamental difference between the optical activity of compounds has led to the development of stereochemistry. The rotatory power of solids is frequently not a property of the individual molecules, but is due to a certain definite arrangement of a number of molecules in the crystalline aggregate, for as soon as the latter is disintegrated (*e.g.*, by solution in water) the action on polarised light ceases. Since tartaric acid, on the other hand, is optically active in solution, this activity must be due to the individual molecules; an assumption of any molecular complexity in this state is entirely disproved by the fact that camphor and certain terpenes, which can be vaporised without decomposition, retain their optical activity unimpaired in the gaseous state.

This view was most clearly expressed by Pasteur, who

in the following words anticipated with remarkable insight the present conception of the relative spatial structure, or as it is now termed *configuration*, of the dextro- and laeo-tartaric acids:—"We know on the one hand that the molecular structures of the two tartaric acids are asymmetric, and on the other that they are rigorously the same, with the sole difference of showing asymmetry in opposite senses. Are the atoms of the right-acid grouped on the spiral of a right-handed helix, or placed at the solid angles of an irregular tetrahedron, or disposed according to some particular asymmetric grouping or other? We cannot answer these questions. But it cannot be a subject of doubt that there exists an arrangement of the atoms in an asymmetric order, having a non-superposable image. It is not less certain that the atoms of the left-acid realise precisely the asymmetric grouping which is the inverse of this."<sup>1</sup>

At this period structural chemistry was in its infancy, and no important advance in regard to the special characteristics and isomeric relations of optically active compounds is recorded until 1874, by which time great strides had been made in the knowledge of the constitution of organic compounds. Some years previously (1869) J. Wislicenus<sup>2</sup> had observed the difference in physical properties, including optical activity, of lactic acid prepared from meat extract and those of an isomer which he had prepared synthetically, two compounds which were absolutely identical in their chemical behaviour. He indeed suggested (1873) that this difference might be due to "the different arrangement of their atoms in space," but it was reserved for van't Hoff and Le Bel (1874) to enunciate, independently of each other, the theory of the asymmetric carbon atom, as the outcome of their studies on optically active organic compounds.<sup>3</sup>

Their theory rested primarily upon the observation that

<sup>1</sup> "Récherches sur la dissymétrie moléculaire des produits organiques naturels," Paris, 1860. Translation published as No. 14 of *Alembic Club Reprints*, 1897.

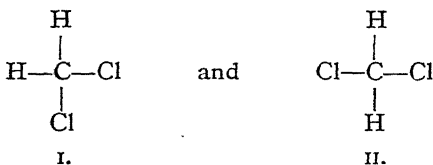
<sup>2</sup> *Berichte*, 1869, ii. 620.

<sup>3</sup> *La Chimie dans l'espace*, J. H. van't Hoff; Le Bel, *Bull. Soc. Chim.*, 1874 [2] xxii. 337. Cf. also J. H. van't Hoff, *Dix années dans l'histoire d'une théorie*, 1887; trans. by J. E. Marsh, *Chemistry in Space*, 1891; and *The Arrangement of Atoms in Space*, trans. by A. Eiloart 1898.

all compounds which rotate the plane of polarised light contain at least one carbon atom united to four different groups or elements, called an *asymmetric* carbon atom. An entirely new field of thought was opened out by this work, inasmuch as it brought into consideration the relative spatial arrangement of the atoms in a molecule. Its object was to explain the isomerism of substances which could not be accounted for by the law of the linking of atoms as hitherto conceived; this law had previously been restricted to two dimensions; van't Hoff and Le Bel extended it to three dimensional space, and thus led up to spatial or stereochemical isomerism.

The theory of the asymmetric carbon atom was first tested in isolated instances with substances which possessed optical activity. Thus, several alcohols and acids and their derivatives, which contained one or more asymmetric carbon atoms, were shown to be optically active.<sup>1</sup> With the development of stereochemistry the theory has been subjected to many severe and thorough tests, and the exact agreement between theory and experiment that has followed leaves no doubt as to the correctness of the views put forward by van't Hoff and Le Bel.

*The Tetrahedron symbol for the Carbon atom.*—The symmetry of the methane molecule,  $\text{CH}_4$ , has already been considered; also the fact that one mono-substitution product, indicated as the only possibility according to the law of the linking of atoms (*e.g.*,  $\text{CH}_3\text{Cl}$ ), is the only one known.<sup>1</sup> But the graphic formulæ previously given as an expression of this symmetry of methane are not in accord with facts when further substitution products of the hydrocarbon are considered. For instance, according to this formula two isomeric methylene dichlorides,  $\text{CH}_2\text{Cl}_2$ , would be possible:—




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<sup>1</sup> Chap. ii. p. 23.



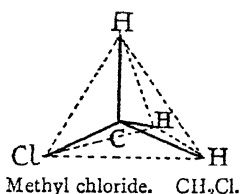
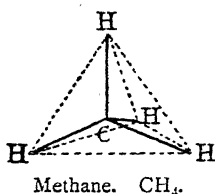
In formula I. the chlorine atoms are next to each other, in II. they alternate with the hydrogen. This indication of such graphic formulæ as expressing the law of the linking of atoms is entirely at variance with the experimental data concerning methylene dichloride and all similar di-substitution products of methane, for in each case only one compound of this type is known.

It is accordingly concluded that such graphic formulæ give an imperfect representation of the symmetrical disposition of the four affinities of the carbon atom; the symmetry is more complete than these formulæ indicate. That graphic formulæ were simply regarded as a plan or diagram of the arrangement of the atoms within a molecule, and not as a representation of the actual relative positions of the substituents, has already been stated. Still, these plane diagrams sufficed to explain the structural relations of molecules until the more refined isomerism of compounds which showed no differences in their chemical behaviour, such as that of the two lactic acids and of the tartaric acids, had been established. The molecules themselves were certainly always regarded as occupying three dimensions, like all other matter, but no attempt to assign spatial relations to their constituent atoms appeared necessary.

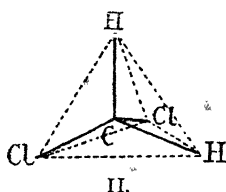
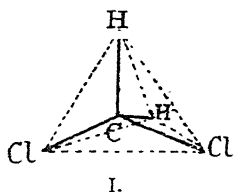
It was the limitations and shortcomings of such graphic formulæ that led van't Hoff and Le Bel to the conception of the tetrahedron as the best representation of the carbon atom affinities; Kekulé (1867) and Paternò<sup>1</sup> (1869), independently, previously hinted the idea of representing the four affinities of the carbon atom by the directions of the axes of a tetrahedron.

The proved symmetry of methane necessitated the choice of a regular geometrical solid; the regular tetrahedron is the simplest and only possible form that can give full expression to this symmetry. The carbon atom itself is regarded as situated in the centre of the tetrahedron, its four affinities being directed towards the four solid angles. The formulæ for marsh gas and methyl chloride, using the tetrahedron symbol, are given below; the real symmetry of the molecules is clearly evident:—

<sup>1</sup> Cf. *Chem. Centr.*, 1908, i. 615.

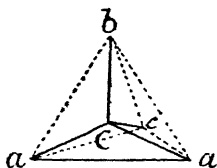


Methylene dichloride is equally symmetrical; the two formulæ I. and II. are really identical, for the figures

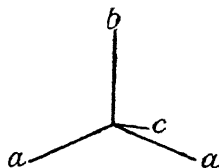


Methylene dichloride.  $\text{CH}_2\text{Cl}_2$ .

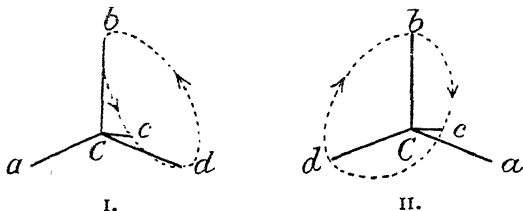
are superposable and have each a plane of symmetry. This symmetry holds for such compounds as  $\text{CHCl}_3$ ,  $\text{CHBrCl}_2$ ,  $\text{CBr}_2\text{Cl}_2$ , and, in fact, for all compounds in which any two of the carbon valencies in methane are satisfied by the same element or group. It ceases, however, as soon as there are four different elements or their equivalent in combination with the carbon atom. The carbon atom under these conditions is unsymmetrically or asymmetrically situated in regard to the four elements or radicals with which it is united; it is this condition of combination, the presence of an asymmetric carbon atom, that van't Hoff and Le Bel recognised in all optically active organic compounds. Suppose  $a$ ,  $b$  and  $c$  represent the substituting groups in a compound of the type  $\text{Ca}_2bc$ , then only one configuration of the molecule is possible, viz.:—



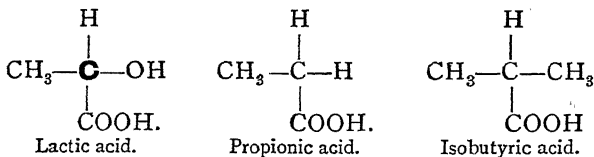
or, in outline, and omitting the symbol for carbon:—



But if one of these groups,  $a$ , be replaced by a new group  $d$ , then two different configurations will result according as the right or left hand group  $a$  is replaced, thus:—



That these configurations are different and in no way superposable is clear from the relative order of the substituents  $b$ ,  $c$ ,  $d$ , as indicated by the dotted lines; in I. they go counter-clockwise, in II. clockwise. No plane of symmetry exists; the two systems are related as the right hand to the left—one is the mirror image of the other, like two enantiomorphous crystals. It is this *stereochemical isomerism* that is regarded as representing the relation of two oppositely active molecules, such as dextro- and lævorotatory tartaric acid, the right-handed and left-handed helix of Pasteur. No difference in chemical behaviour would be expected from this stereochemical difference; all observed differences amongst such isomers are restricted to physical properties, especially to the direction of the rotation of polarised light. No optically active compounds are known which do not contain an asymmetric atom or group of atoms; this is the all-convincing proof of the correctness of the views of van't Hoff and Le Bel, and as soon as the asymmetry of a molecule is destroyed by substitution, the optical activity is also removed. Thus, lactic acid has an asymmetric carbon atom, indicated below in thick type:—

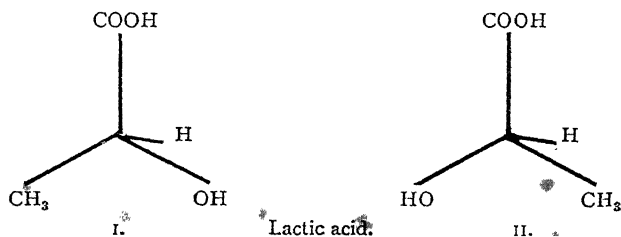


but neither propionic nor isobutyric acid, which are derived from it by substituting the hydroxyl by hydrogen

or by methyl respectively, are optically active. The latter are both symmetrical compounds.

Whilst, without exception, all optically active compounds contain an asymmetric atom or group, the reverse does not hold. Of the two lactic acids already referred to, that obtained by the fermentation of sugar or prepared by synthetical methods in the laboratory is optically inactive, whilst the acid previously discovered by Liebig in meat-extract is dextro-rotatory. Both contain the asymmetric carbon atom, to which the other atoms and radicals of the molecule are similarly linked; the relation is analogous to that of tartaric and racemic acids. Since racemic acid can be split up into the optical antipodes by the fractional crystallisation of suitable salts, it is regarded as a combination, in molecular proportions, of the two oppositely active forms; this holds in regard to the inactivity of all racemic compounds. Inactive lactic acid can be similarly decomposed by the fractional crystallisation of suitable salts, and in this way lævo-rotatory lactic acid has been prepared.<sup>1</sup> There are, therefore, three forms of lactic acid of which the right- and left-handed are really different, whilst the inactive form is a combination of the other two. This fact is well illustrated by mixing solutions of the zinc salts of the two active acids, each of which contains two molecules of water of crystallisation and are fairly soluble in water, when the more sparingly soluble zinc salt of the inactive acid, containing three molecules of water of crystallisation, separates.

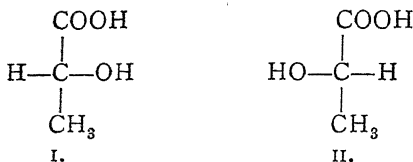
This isomerism of the two lactic acids is shown in the following formulæ:—



<sup>1</sup> Purdie and Walker, *J. Chem. Soc.*, 1892, ix. 754.

No means are known for deciding the order of the substituents in either molecule. As their arrangement is purely relative, it is immaterial which of the two configurations is assigned to the dextro-rotatory acid; in either case the reflex will represent the lævo-isomer.

For the concrete study of these stereochemical relations suitable models are employed which, both for the student and the investigator, are a considerable aid in the recognition of the geometrical relations that arise, especially amongst the more complex compounds. In order to represent these relations on paper it is unnecessary to draw the formulæ on the tetrahedron model as above, since the isomerism is equally clear if a projection of the model in the plane of the paper be used; this is the method generally adopted to show the relations of stereochemical isomers. The following projection formulæ for the lactic acids illustrate the advantage of this simplification:—



Projected stereochemical formulæ for the lactic acids.

The relative position of the hydrogen and hydroxyl to the two other substituents is obviously reversed in the two formulæ; they are the reflex of each other, but it is to be borne in mind that these are projected formulæ of the tetrahedron symbol, and not the old two-dimensional, graphic representations.

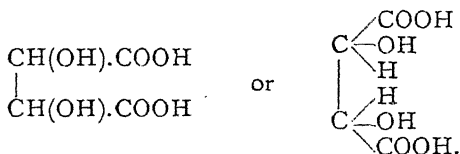
Although, generally speaking, every optically active compound contains an asymmetric atom, optically active compounds are known in which no individual carbon atom is asymmetric, but the atoms of which are grouped together in such a way that the molecule contains no plane of symmetry.<sup>1</sup> This exceptional condition of optical activity occurs with the carbohydrate *inositol*, a derivative

<sup>1</sup> Cf. Maquenne, *Ann. Chim. Phys.*, 1890, [6] xxii. 264; Bouveault, *Bull. Soc. Chim.*, 1894, [3] xi. 144; Marckwald and Meth, *Berich* 1906, xxxix. 1171.

of hexamethylene; the carbon atoms form an asymmetric ring, and although no carbon atom is joined to four different groups, the compound exists in a dextro- and lævo-, as well as in the inactive-form. This forms no contradiction to the theory of the asymmetric carbon atom; indeed, van't Hoff foresaw, in his original exposition of the theory, that such groups of atoms could give a similar effect to that of a single asymmetric atom.

*The Stereochemistry of the Tartaric Acids.*—In so far as optically inactive compounds containing an asymmetric carbon atom represent a combination of oppositely active forms, the stereochemical theory has been shown to be quite satisfactory, but it has still to account for the fourth tartaric acid, inactive or meso-tartaric acid, which cannot be split up into two stereochemical isomers.

A few of the properties of these acids may be advantageously considered first. The four acids, dextro-tartaric, lævo-tartaric, meso-tartaric, and racemic show very few differences in their chemical behaviour. There is ample proof that they are all dibasic, dihydroxy-acids of the same molecular formula,  $C_4H_6O_6$ , the linking of the constituent groups being represented graphically as follows:—



Tartaric acid.

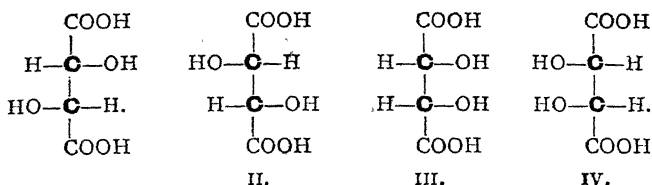
The dextro- and lævo-rotatory acids differ only in their action on polarised light and in the position of the hemihedral faces on their crystals; in all other respects they are exactly alike. They melt at the same temperature, are equally soluble in water, and their salts, apart from the above optical and crystallographic differences, are in every respect similar; derivatives such as the esters melt and boil at the same temperature. Racemic acid, on the other hand, presents more marked differences. Its crystalline

form is triclinic, whilst the above acids crystallise in the monoclinic system, and it contains water of crystallisation, whilst the active acids are anhydrous; both the free acid and its calcium salt are less soluble in water than tartaric acid and calcium tartrate respectively, and dimethyl-racemate melts considerably higher than the isomeric tartaric ester. Meso-tartaric acid, like racemic acid, crystallises with one molecule of water of crystallisation, but its solubility in water is about equal to that of dextro- and lævo-tartaric acid; on the other hand, it forms a characteristic acid potassium salt, which is much more soluble than the corresponding salt of its isomers, and the diethyl ester is a solid, whilst the active diethyl-tartrates and diethyl-racemate are liquids.

In addition to these differences in physical properties, the tartaric acids are characterised by the ease with which they can be converted one into the other. When dextro-tartaric acid is heated to  $175^{\circ}$  in presence of a little water, it is gradually converted into racemic acid, and this conversion is practically complete in thirty hours. At a slightly lower temperature ( $165^{\circ}$ ) meso-tartaric acid is formed, together with racemic, and the former is itself partially transformed into the latter on heating. Such mutual transformations are a special characteristic of stereochemical isomers, and the repeatedly observed phenomenon that optically active compounds lose their activity upon heating is an example of a similar change, resulting in the formation of an inactive isomer or of a racemic combination.

Turning now to the stereochemical relations of these four acids, the above graphic formula shows that their molecules contain two asymmetric carbon atoms, each in combination with a hydrogen, hydroxyl, and carboxyl, the fourth affinity of each carbon atom serving to link the two halves of the molecule together, as in ethane. The possibilities of stereochemical isomerism are naturally, therefore, more numerous than in the case of lactic acid, which contains only one asymmetric atom. When the possible disposition of the six substituents is studied on the tetrahedron models, there appear at first sight to be four configurations possible; the projected formulæ are as follow:—

# STEREOCHEMISTRY.



The actual disposition of the atoms and groups in these four formulæ is best followed by regarding their order in the two halves of each molecule separately. If the link between the two carbon atoms in I. be separated on a model, it will be seen that the two halves of the molecule exactly superpose each other, the order of the substituents H, OH, COOH being the same in both when looked at from the same position. Hence, if it be supposed that polarised light, entering the molecule from above, receives a right-handed twist from the upper portion of the molecule, this twist will be supplemented by the lower half; the whole will, therefore, be optically active—say, dextro-rotatory. Formula II. will similarly represent an optically active molecule, but the order of the substituents is the opposite to that of I., and the entering polarised light will be twisted in the opposite direction; the molecule will be lævo-rotatory. Each is a reflex of the other, and these configurations are obviously to be assigned to the two active tartaric acids. They represent an enantiomorphous pair, which, when mixed in molecular proportions, produce the inactive form, racemic acid. Applying similar considerations to formulæ III. and IV., both will be seen to be inactive, and moreover identical. The order of the three substituents in the two halves of the molecule is opposite; the twist given to polarised light in the upper half of the molecule will therefore be reversed in the lower, and optical inactivity will result. This *internal* or *intra-molecular* compensation, which is represented by the configurations III. and IV., is the cause of the inactivity of meso-tartaric acid. Such a molecule evidently cannot be divided into its optically active isomers, as in the case of racemic acid, which is inactive by *external* or *inter-molecular* compensation, because two equal and opposite asymmetric groups are contained within the same molecule.



These relations of the four acids can be summarised as follows, *d* and *l* representing the opposite optical activities of the two portions of the molecule:—



The constitutional difference between the two inactive forms of tartaric acid receives, therefore, a complete explanation from the standpoint of the stereochemical theory; similar relations exist amongst other compounds containing two asymmetric carbon atoms.

A comparison of the above configurations of dextro- and lævo-tartaric acids indicates that the relative distance of each atom or group from the others is correspondingly the same, and hence the same condition of equilibrium will exist in the two molecules. In meso-tartaric acid, on the other hand, the same atoms and groups are differently situated in respect to each other, and they cannot under any conditions be so arranged as to show the same conditions of equilibrium that obtains with the active acids. Its isomeric relation to the latter is, therefore, distinctly less subtle in character than that between the two active acids, and this difference finds its equivalent in their relative physical properties referred to above.

The nature of the combination of the two active acids in racemic acid is not decided. Although often spoken of as a mixture, it is more probable that some degree of combination exists between the two molecules, for it would be strange if the mere admixture of two compounds, so alike in all their properties as the two active acids, were to form a product showing marked differences from its constituents in physical properties, apart from its optical inactivity. These differences are essentially concerned with the solid state, for racemic acid and its derivatives when in solution or in the liquid or gaseous state behave like a normal mixture.

The mutual transformations of the tartaric acids by the action of heat can be advantageously studied in the light of the stereochemical formulæ. To convert dextro-tartaric acid into racemic acid, for instance, the configuration of

one-half of the total number of molecules must be changed. This change is to be attributed to the more violent atomic vibrations within the molecule at higher temperatures. It is unlikely that this change proceeds in one direction only; most likely the lævo-rotatory molecules formed will also be transformed into their antipode, and thus from their side contribute to the formation of the racemic form. Final equilibrium, assuming that the change proceeds equally easily in either direction, which is extremely likely, will be reached when the number of right- and left-handed molecules is equal—*i.e.*, the original acid has been completely racemised. It is also evident that no excess of left-handed molecules will be formed during the transformation. The formation of meso-tartaric acid is to be attributed to similar atomic movements within the molecule, but in this case they must be restricted to a change of configuration in only one-half of the tartaric acid molecule. There are no special conditions of equilibrium that might arise, and, as a matter of fact, a mixture of meso-tartaric acid, racemic acid, and dextro-rotatory tartaric acid is formed when the ordinary (dextro-rotatory) acid is heated to the lower temperature ( $165^{\circ}$ ). The tartaric acid that remains in the final mixture is generally spoken of as "unchanged," but this is not necessarily the case. Active tartaric acid can also be racemised by the action of alkalis, and in this case it has been shown<sup>1</sup> that the change takes place in two successive stages; one asymmetric carbon atom is first affected, forming the meso-acid, and the change then completed by a change in the configuration of the groups attached to the second asymmetric carbon atom. A condition of equilibrium is finally attained as explained above.

The stereochemical relations of the tartaric acids are typical of those of all similarly constituted substances; two active and one inactive compound can exist and one racemic combination. When the substituting groups in the two parts of a molecule containing two asymmetric carbon atoms are dissimilar, the number of stereochemical isomers is increased; two active and two inactive forms become possible, together with two racemic combinations. With an increase in the number of asymmetric carbon

<sup>1</sup> Winter, *Z. physik. Chem.*, 1906, lvi. 466, 720.

atoms the conditions of stereochemical isomerism become more complex, and the assigning of the configuration is then a very difficult task. These conditions will be considered in connection with the sugars (Chapter XIII.), the group in which the hypothesis of van't Hoff and Le Bel has received its most complete and convincing support.

*Racemic Combinations and their Resolution into Optically Active Compounds.*—Racemic acid and all similar externally compensated combinations are distinguished from their optically active isomers by their crystalline form and specific gravity, and usually by a difference in solubility and melting point. These same physical properties serve to distinguish racemic combinations from mere mixtures;<sup>1</sup> in the latter each component retains its own physical properties, and can usually be mechanically separated from its antipode. Whilst this distinction is comparatively easy in the case of most solids, although various grades of racemic combination appear to exist,<sup>2</sup> no means are at present known for distinguishing racemic liquids from inactive mixtures.

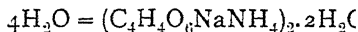
A further characteristic of racemic combinations is the fact that it is possible to resolve them into their optical isomers, a discovery due to Pasteur (1848), who succeeded in working out no less than three distinct methods for this purpose. These methods have since been applied to the resolution of numerous racemic combinations; they have been elaborated and improved, but no further methods have been added during the sixty years which have elapsed since their discovery.

The first of these methods is that mentioned in connection with racemic acid itself, the crystallisation of a suitable salt. By careful evaporation of a solution of sodium ammonium racemate below 27°, the crystals that separate consist of the salts of the dextro- and lævo-tartrates, which can be distinguished by the position of their hemihedral faces, and thus be mechanically separated from each other. This is because below 27° sodium ammonium racemate, which crystallises with two molecules of water of crystallisation, takes up water to form the dextro- and lævo-

<sup>1</sup> Cf. Stewart, *Stereochemistry*, p. 37.

<sup>2</sup> Cf. Kipping and Pope, *J. Chem. Soc.*, 1897, lxxi. 989; and Roozeboom, *Z. physik. Chem.*, 1899, xxviii. 498.

tartrates, each of which crystallises with four molecules of water of crystallisation; above this temperature, which is called the *transition temperature*, the tartrates lose water and form the racemate, a change which may be expressed by the equation<sup>1</sup>:—



*d* and *l*. Sodium ammonium tartrates. Sodium ammonium racemate.

There is similarly a definite transition temperature for all other racemic compounds, above which the active constituents are converted into the racemic combination. The zinc-ammonium salt of inactive lactic acid can be thus resolved into the two active forms, and in some cases the simple evaporation of an ethereal solution will effect the separation of enantiomorphous crystals.<sup>2</sup> Owing to the equal solubility of the dextro- and lævo-forms, the separation of the two always takes place in equal proportions. But by effecting the crystallisation from an optically active solvent a change in this equivalent separation of the two antipodes is sometimes possible, owing to their having a different solubility in the asymmetric solvent. Thus, Kipping and Pope<sup>3</sup> have shown that dextro-sodium ammonium tartrate is less soluble than the lævo-salt in a concentrated solution of glucose (which is dextro-rotatory) at the ordinary temperature, a property which allows consequently of the separation of the enantiomorphs by fractional crystallisation. This is an important extension of Pasteur's method. The equal solubility of the optical isomers in ordinary solvents may thus be changed if the solvent be itself an asymmetric substance.

An analogous influence is at the basis of the other methods for the resolution of racemic combinations. Thus in the second method originated by Pasteur the separation of the isomers is effected by combining the racemic compound with an asymmetric base or acid to form a salt. Pasteur recognised that whereas the constituents of an externally compensated compound like racemic acid will possess equal affinities for a symmetric base such as

<sup>1</sup> Cf. Van't Hoff and Deventer, *Z. physik. Chem.*, 1887, i. 165.

<sup>2</sup> This occurs with Isohydrobenzoin, *Berichte*, 1897, xxx. 1531.

<sup>3</sup> *J. Chem. Soc.*, 1898, lxxiii. 606.

potassium or sodium hydroxide, a difference will be introduced if the combination be effected with an asymmetric base, with the result that the salts should show differences in solubility and in other physical properties, which should serve for their separation.

This method depends upon the general consideration that when a combination of two optically active acids, such as *d*- and *l*- tartaric acid, is effected with an optically active base, a mixture of two salts is obtained which are no longer enantiomorphously related. Calling the acid, A, and the base, B, the salt of the dextro-rotatory acid will be *d*-A.*d*-B, that of its isomer *l*-A.*d*-B, the base being taken as dextro-rotatory. A difference is thus clearly introduced, with which the above differences in physical properties are associated. The preparation of the free acids from such salts is easily carried out and thus the separation of the enantiomorphs effected.

Pasteur resolved racemic acid by forming a salt with the alkaloid cinchonine, an asymmetric base; on allowing the solution of this salt to crystallise, the salt of the lævo-tartrate separated first, being more soluble than that of the dextro-tartrate. The crystalline form of the two salts was also quite distinct.

A number of other alkaloids, such as quinine, brucine and strychnine, have been found most valuable for thus resolving the inactive combinations of acids; the resolution of inactive lactic acid, for instance, was effected by means of the strychnine salts, that of the lævo-acid being less soluble than strychnine dextro-lactate.

Optically active acids can be similarly employed for the resolution of racemic bases. Dextro-tartaric acid was successfully employed for this purpose by Ladenburg in the preparation of optically active conine, the first synthetically prepared alkaloid,<sup>1</sup> and more recently by Pictet and Rotschy in their synthesis of nicotine.<sup>2</sup> Tartaric acid has also been applied in several other instances, but it is a comparatively weak acid, and its salts, especially with weak bases, are less stable and less well-defined than those of stronger acids. The advantage of using stronger asymmetric acids has been recognised and

<sup>1</sup> Cf. Chap. xv. p. 409.

<sup>2</sup> *Bull. Soc. Chim.*, 1904, [iii.] xxxi. 317.

practised by Pope<sup>1</sup> with remarkable success. By the use of a dextro-rotatory sulphonic acid of camphor he has been able to resolve the racemic combinations of a number of weak bases of which the active forms were previously unknown, and also to establish the asymmetric nature of compounds of other elements than carbon; these will be referred to subsequently.

Pasteur's third method, which was the stepping-stone to his great work on ferments, effects the separation of enantiomorphs by means of the asymmetric, living organism. From the standpoint that optical isomers showed a difference in behaviour towards a third asymmetric compound, Pasteur studied the action of an enzyme, *Penicillium glaucum*, on a solution of ammonium racemate. He found that fermentation took place just as it did in the case of ammonium tartrate, but that the solution of the inactive salts became lævo-rotatory, and that the optical activity gradually increased up to a maximum, when the fermentation ceased. The lævo-tartrate was obtained in a state of purity from the residual solution; the dextro-tartrate was completely destroyed. This same enzyme resolves the salts of many other acids, such as the inactive forms of lactic, glyceric, malic and mandelic, and in each case the residual acid is lævo-rotatory. Other enzymes and a variety of bacteria act similarly, but they show differences in respect to the isomeride that is left in excess after their growth. In all cases either one enantiomorph is destroyed and the other left, or if both are attacked, one is decomposed more rapidly than the other.<sup>2</sup> The asymmetric living organism possesses the power of discriminating between the two active forms, choosing one, either solely or preferably, for its own nutriment, a choice probably regulated by its own asymmetry. Certainly these low forms of life exercise the most remarkable particularity in respect to the geometrical structure of their food molecules, a point which is emphasised in connection with the sugars.<sup>3</sup> It may be noted that fermentative changes do not necessarily result in the formation of optically active compounds; inactive

<sup>1</sup> *J. Chem. Soc.*, 1899, lxxv. 1105.

<sup>2</sup> *Cf.* McKenzie and Harden, *J. Chem. Soc.*, 1903, lxxxiii. 424.

<sup>3</sup> *Cf.* Chap. xiii. p. 343.

lactic acid, for instance, is obtained by the action of the lactic acid ferment upon sugars, and there are other examples.

*The Synthetical Preparation of Optically Active Compounds.*—All naturally occurring compounds which contain an asymmetric carbon atom are characterised by optical activity. Grape sugar is dextro-rotatory, fruit-sugar lævo-rotatory; both dextro- and lævo-rotatory terpenes are found in nature, whilst amongst many complex molecules of unknown structure, such as alkaloids and proteins, asymmetry as evidenced by optical activity has long been recognised. Pasteur in his "Lectures on the Molecular Asymmetry of Natural Organic Products," given before the Chemical Society of Paris in 1860,<sup>1</sup> refers to this "molecular asymmetry of natural organic products" as "the great characteristic which establishes perhaps the only well-marked line of demarcation that can at present be drawn between the chemistry of dead matter and the chemistry of living matter." Whether this line of demarcation still holds will be considered in Chap. XIII. Meanwhile, it is a thoroughly recognised and established fact that in all synthetical processes as carried out in the laboratory from symmetric compounds inactive products alone result. These may be inactive either by external or by internal compensation. In the former case the racemic combinations may be resolved by the methods just described, but in no case is a single active compound the direct result of a laboratory synthesis from symmetric compounds. For instance, in that of tartaric acid from ethylene *via* succinic acid and dibrom-succinic acid,<sup>2</sup> a mixture of racemic and meso-tartaric acid results; other synthetical methods lead to racemic acid only. Similarly, when lactic acid is prepared from acetaldehyde by the action of hydrocyanic and subsequent hydrolysis,<sup>3</sup> or from propionic acid, the resulting product is the racemic combination.

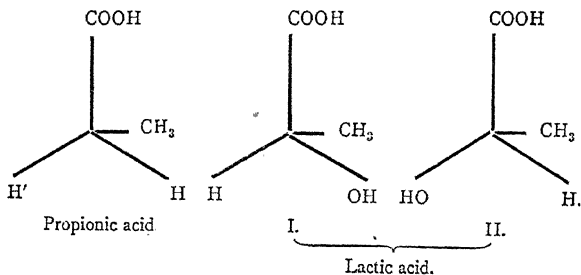
The cause of this is not far to seek. In all these syntheses a previously symmetrical molecule is rendered asymmetric by the introduction of the new substituent,

*Alcmbic Club Reprints*, No. 14, 1897.

<sup>2</sup> Chap. viii. p. 153.

<sup>3</sup> Chap. viii. p. 138.

and obviously the dextro-compound can be formed just as easily as the lævo-form, and accordingly equal quantities of the two result. Thus, in the formation of lactic acid from propionic acid, either of the hydrogen atoms, represented on the subjoined tetrahedron formula by H. and H', may be replaced by hydroxyl; the forces concerned in the introduction of the new substituent are undirected, and consequently the chances of either point of attack being chosen are equal. Formula I. for lactic acid represents the molecule formed by the replacement of H by hydroxyl, formula II. by that of H'. They form an enantiomorphous pair, and being produced in equal quantities, constitute a racemic combination :—



Racemic acid results on analogous lines. In meso-tartaric acid the conditions of equilibrium in the molecule are different, as already explained, and it may or may not be formed in synthetical processes. All the synthetical methods employed for the preparation of asymmetric compounds from symmetric compounds are of this type; the initial symmetric compounds give two equivalent points of attack, with the result that an equal number of molecules of the two possible stereo-isomers are formed.

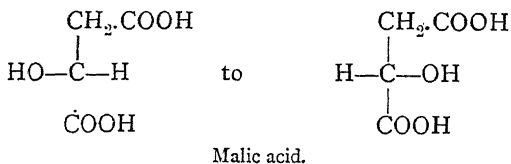
The resolution of these inactive combinations by one or other of the methods described has not always proved possible, especially in the case of compounds which show no marked basic or acid properties, such as brom-nitroethane, CH<sub>3</sub>.CH.Br.NO<sub>2</sub>, but Pope's recent success in the resolution of weak bases justifies the view that a further



extension of the old methods is likely to lead to successful results with other racemic combinations.

An important discovery bearing on the synthetical preparation of optically active compounds was made by Walden (1896), who showed that two enantiomorphously related compounds could be mutually transformed without the intervention of the racemic combination.<sup>1</sup>

For instance, *d*-malic acid, which contains one asymmetric carbon atom, when treated with phosphorus pentachloride is converted into a chlorsuccinic acid which, whilst it has the same configuration as the original acid, is oppositely active; although lævo-rotatory, it is called *d*-chlorsuccinic acid so as to record its relation to *d*-malic acid. Similarly, *L*-malic acid yields *L*-chlorsuccinic acid which is dextro-rotatory. When these chlorsuccinic acids are treated with strong bases, such as sodium or potassium hydroxide, the malic acid from which they were prepared is regenerated in each case; but with weak bases, such as silver oxide or mercuric oxide, they yield the opposite enantiomorph—*i.e.*, the configuration is changed from:—

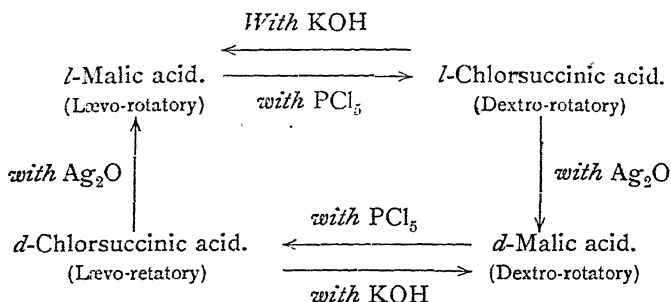


or vice versa.

The following diagram represents this remarkable cycle of changes. It has been suggested that the different action of strong and of weak bases on the halogen succinic acids is due to a difference in the mechanism of the change, that of the former being a direct replacement of halogen by hydroxyl, whilst in the case of weak bases symmetric addition compounds are formed, an atom or group of which has a directing force in respect to the configuration of the new molecule.<sup>2</sup>

<sup>1</sup> Cf. *Berichte*, 1899, xxxii. 1855.

<sup>2</sup> Cf. Walden, *Berichte*, 1899, xxxii. 1833; Armstrong, *J. Chem. Soc.*, 1896, lxix. 1399.



*Asymmetric Synthesis.*—Whilst inactive products always result in the synthesis of organic compounds from symmetric substances, the conditions are obviously different if a carbon atom be rendered asymmetric, by substitution, in a molecule already containing an asymmetric carbon atom; the asymmetry already present may then influence the conditions under which the new asymmetric carbon atom is formed in such a way as to lead to the formation of only one, or of an excess of one, of the two possible stereo-isomers. The first attempts to effect "asymmetric syntheses" of this character were unsuccessful, but E. Fischer and Slimmer,<sup>1</sup> and especially A. McKenzie,<sup>2</sup> have now proved that the directing influence of an optically active group causes the preferential formation of an optically active derivative. The method adopted by McKenzie was to prepare an optically active derivative of a symmetric compound such as a ketone, then to reduce this to the corresponding alcohol whereby a new asymmetric carbon atom was formed, and finally to eliminate the original optically active portion of the molecule.

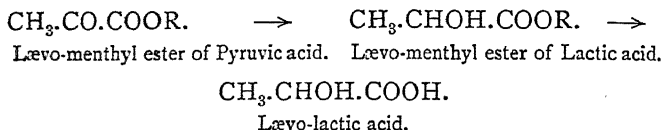
For example, when the ketonic acid, pyruvic acid is reduced to lactic acid one of the carbon atoms is rendered asymmetric; the product obtained, however, is the racemic combination of dextro- and lævo-lactic acids as in all other similar syntheses.

<sup>1</sup> *Berichte*, 1903, xxxvi. 2575.

<sup>2</sup> *J. Chem. Soc.*, 1904, lxxxv. 1249; 1905, lxxxvii 1373; 1906, lxxxix 365; 1907, xci. 1215.



If, however, the pyruvic acid be first combined with an optically active alcohol to form an ester, the latter then similarly reduced and the ester of the alcohol thus obtained partially saponified by an insufficient quantity of alkali, the resulting lactic acid is optically active, owing to the presence of a slight excess of one of the stereo-isomers. The optically active alcohols lævo-borneol and lævo-menthol were used by McKenzie in these experiments. These changes may be expressed by the following formulæ, in which R represents the asymmetric radical of borneol or menthol:—



Such asymmetric syntheses are of especial interest on account of their bearing upon the natural synthesis of active compounds.<sup>1</sup>

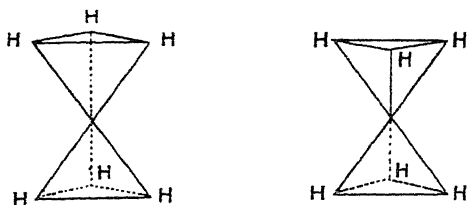
*The Geometrical Isomerism of Unsaturated Compounds.*—The stereochemical relations so far considered are restricted to compounds containing one or more asymmetric carbon atoms. Other cases of unexplained isomerism had long been known and studied, especially that of two unsaturated compounds, fumaric and maleic acid. Van't Hoff was the first to suggest that they were stereochemical isomers, a view which is now generally accepted, whilst J. Wislicenus (1887) developed the general principles underlying the stereochemical relations of such unsaturated organic compounds.<sup>2</sup> The term *Geometrical Isomerism* is now generally used to distinguish the space isomerism of

<sup>1</sup> Cf. Chap. xiii. p. 357.

<sup>2</sup> *Ueber die räumliche Anordnung der Atome in organischen Molekülen*, 1887. Published by Hirzel, Leipzig.

substances of this character from that associated with molecular asymmetry. In outline, the principles brought forward by Wislicenus are as follows.

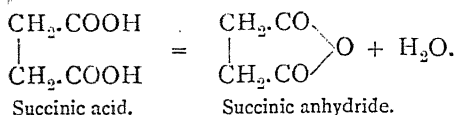
When two carbon atoms, as represented by the tetrahedron symbol, are united by a single bond, as, for instance, in ethane, each carbon atom is free to rotate about this bond. Hence, it is indifferent whether the direction of each valency of the first carbon atom is represented as vertically above each valency of the second, or whether it is placed in an intermediate position, as in the following formulæ:—



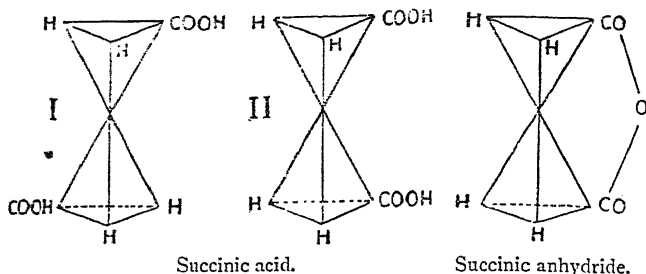
Ethane.

In either case by a slight rotation of one of the carbon atoms the two molecules become identical. If this were not the case—that is, if the linking between the carbon atoms were rigid, a large number of isomeric ethanes, differing slightly in their properties according to the relative positions of the hydrogen atoms, should be possible, but there is no evidence whatever of their existence. If the substituents are different, as, for example, in ethylene dichloride,  $\text{CH}_2\text{Cl}.\text{CH}_2\text{Cl}$ , the hydrogen and chlorine atoms will exert a certain attraction for one another and will determine the position of greatest stability, the “favoured configuration”; but even in this case an oscillation about this position will occur, and so a proportion of the molecules may momentarily take up the least favoured configuration under the influence of heat or other added energy. Unless, however, there is some cause to fix the system in this least stable form, it will revert to the most favoured configuration when the added energy is withdrawn. Succinic acid, for instance, which is a compound of similar type to ethylene dichloride,

forms an anhydride when rapidly distilled, according to the equation:—



Of the two extreme stereochemical formulæ:—

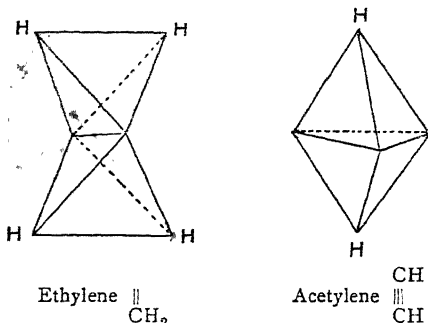


I., in which the carboxyl groups are as far away from each other as possible is the more stable configuration, whilst in II. the carboxyl groups are obviously more favourably disposed for the formation of an anhydride. The former is, therefore, regarded as representing the free acid under ordinary conditions; but when heated it will have a tendency to assume the less favoured configuration which becomes fixed in the formation of the anhydride. The relative stability of the two configurations is also influenced by the introduction of substituting groups; thus, the alkyl derivatives of succinic acid form anhydrides more readily than succinic acid itself, and the more alkyls that are introduced, the greater is the ease with which the separation of water occurs. Trimethyl- and tetramethylsuccinic acid, for instance, form anhydrides almost spontaneously, so that the presence of alkyl groups is clearly favourable to the second of the above configurations.<sup>1</sup>

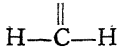
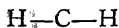
When two carbon atoms are united by a double or triple bond the possibility of free rotation of each portion of

<sup>1</sup> Cf. Bischoff, *Berichte*, 1891, xxiv. 1048; Zelinsky, *Berichte*, 1891, xxiv. 3997.

the molecule, which is the characteristic of singly-linked carbon atoms on the tetrahedron symbol, ceases. In ethylene, for example, the two tetrahedra have an edge in common, in acetylene a face in common, as shown in the following stereochemical formulæ, and the rotation of one half of the molecule relatively to the other is impossible.



This view of the multiple linking of carbon atoms is supported by the fact that the possible geometrical isomers, which are theoretically indicated for a large number of compounds containing a doubly-linked carbon atom, are actually known, and included amongst these are the cases of isomerism amongst unsaturated compounds which were previously unexplained. No isomers are theoretically possible in the case of compounds containing trebly-linked carbon atoms, and none are known. The projection formulæ used for representing the structure of ethylene and acetylene from this standpoint are as follows:—



Ethylene.

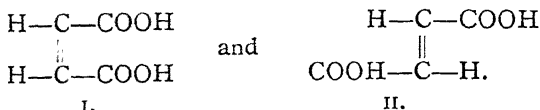


Acetylene.

On the model, the plane occupied by the four valencies of the carbon atoms of ethylene, which are attached to the four hydrogen atoms, is situated at a right angle to the plane of the paper.

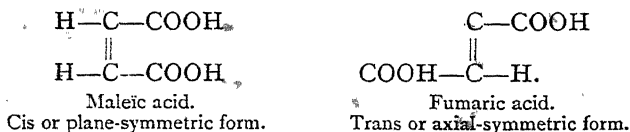
If two of the four hydrogen atoms in ethylene are

symmetrically substituted either by the same or by different elements or radicals, two configurations are always possible. Thus, in the case of fumaric and maleïc acids,  $C_2H_2(COOH)_2$ , already referred to, both of which have the same structural formula, their geometrical isomerism is expressed by the following projection formulæ:—



These formulæ have as yet offered the best explanation of the isomerism of the two acids. As space formulæ they differ in respect to the position of the substituents on either side of the double bond and such difference is obviously less subtle than that existing between an object and its reflex, which occurs with enantiomorphs containing an asymmetric carbon atom. Geometrical ethylenic isomers of this character are in no sense asymmetric, and both optical activity and enantiomorphous, crystalline relations are accordingly excluded. This greater distinction finds its equivalent in the marked differences in the properties of maleïc and fumaric acids. Their properties have already been considered, also the differences in their chemical behaviour and the fact that they are characterised by the readiness with which each may be converted into the other.<sup>1</sup>

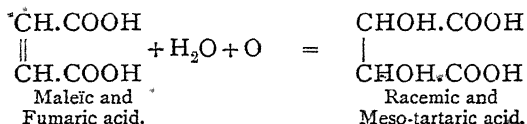
Since maleïc acid forms an anhydride, whilst fumaric acid does not, and also on account of the greater stability of the latter, the allotment of the two stereochemical formulæ presents no difficulty. That with the two carboxyl groups on the same side evidently corresponds best to the properties of maleïc acid, whilst the form in which the like groups are as far apart as possible will represent the more stable fumaric acid:—



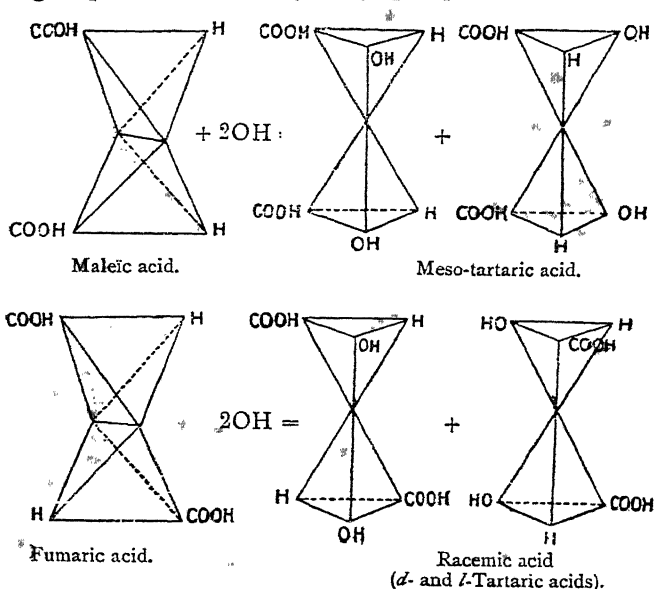
<sup>1</sup> Chap. viii. p.

The terms "cis" and "trans" are generally used to express the relations amongst the atoms or groups in such geometrical isomers.

On oxidation both maleïc and fumaric acids give inactive tartaric acid, but in the case of fumaric acid the resulting product is racemic acid, whilst maleïc acid yields the internally compensated meso-tartaric acid. This is quite in accordance with the stereochemical formulæ given above. The oxidation, which consists in the addition of two hydroxyl groups, is represented by the equation:—



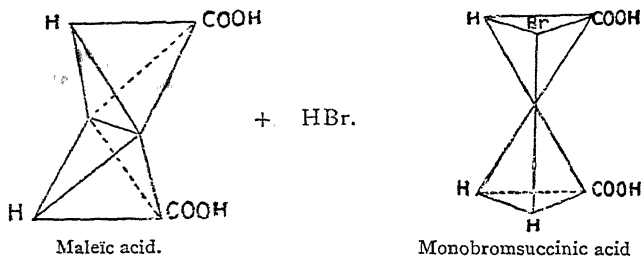
On the basis of the tetrahedron model for the formulæ of the two acids, the oxidation products will result as follows, when one or other of the two linkings is broken to give place to the two hydroxyl groups:—



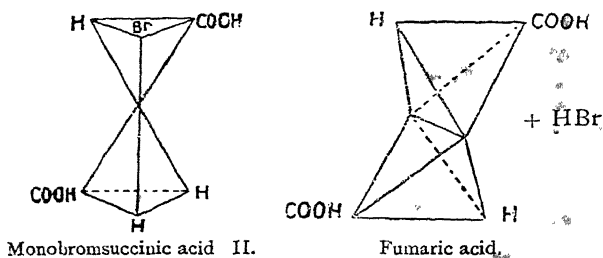


This agreement between the theoretical and experimental results forms an interesting connecting link between the two forms of stereo-isomerism, and affords a strong confirmation of the correctness of the theory of stereochemistry as based upon the tetrahedron symbol for the carbon atom.

To explain the mutual changes of fumaric and maleïc acid, Wislicenus assumed the formation of an intermediate saturated compound. The two halves of such compounds being free to rotate about their common axis would take up the position of maximum stability and by the subsequent separation of the added molecule could form a compound having a different configuration from the original. According to this view, the conversion of maleïc acid into fumaric by the action of hydrobromic acid takes place through the following stages:—



Since a double bond is broken in this change, the added atoms (H and Br) should take up their position on the same side of the molecule (formula I.). But this is the least favoured configuration for such a compound; it will consequently rotate to the most favoured position (formula II.), and from this, by loss of hydrobromic acid, it might pass into fumaric acid:—



The hydrobromic acid is liberated again in the second stage of the reaction, thus explaining why only a small quantity of such a reagent is required to change a comparatively large quantity of maleïc acid into its isomer.

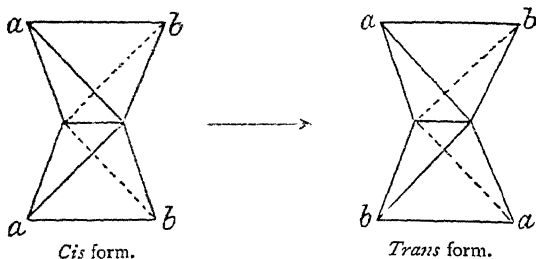
Attractive as this view is, it unfortunately lacks experimental confirmation. No indications of the formation of such intermediate products as the above bromsuccinic acid have been observed, nor are they the unstable compounds required by Wislicenus' interpretation of these changes; monobromsuccinic acid, for instance, is markedly stable and shows no tendency to give up hydrobromic acid at the temperature at which the isomeric change occurs. Moreover, it has been shown that neither the addition nor the separation of halogens and halogen acids with unsaturated compounds always follows on the lines to be expected from the stereochemical formulæ, the *trans* form being produced in some cases where the *cis* form would be expected, and vice versa.<sup>1</sup> Many of the methods of formation and reactions of maleïc and fumaric acid are well accounted for by Wislicenus' views, but their mutual transformations require some other explanation. These isomeric changes occur both with the free acids and with many of their derivatives, not only in presence of added substances such as the halogens and halogen acids, but also upon heating and on exposure to light.<sup>2</sup> It is, accordingly, very probable that such reagents act catalytically as accelerators of a change that can be effected, although more slowly and less completely, without them.

A consideration of the stereochemical formulæ given below for a *cis* and *trans* ethylene compound shows that for the one to change into the other, either the two substituents *a* and *b* must exchange places directly, or that the double bond must be broken and be re-formed in a new position. The former possibility is highly improbable; the latter involves the separation of one carbon affinity, as represented by the junction of an angle, in each of the tetrahedra, followed by a rotation through 180° and the subsequent formation of a new double bond.

<sup>1</sup> A. Michael, *J. Chem. Soc. Abstracts*, 1893, lxiv. 144; and 1896, lxx. 130.

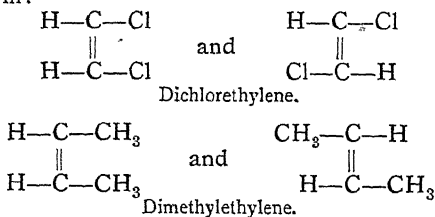
<sup>2</sup> Paal and Schulze, *Berichte*, 1902, xxxv. 168.

# MODERN ORGANIC CHEMISTRY.



Such a change implies that the fixity of position indicated by the double bond is not absolute, but that it may be broken or strained if the conditions are favourable. Experiments by Skraup<sup>1</sup> give some support to this view of the change, but a more complete knowledge of the nature of a double bond between two carbon atoms, and of the essential difference between this and a single bond, is undoubtedly necessary before these isomeric changes can be satisfactorily explained. Meanwhile, however, there is no reason to doubt the correctness of the stereochemical relation of maleic and fumaric acids.

Very many other instances of isomerism are now known amongst unsaturated organic compounds, almost all of which are inexplicable from any other standpoint than that of geometrical isomerism; but, on the other hand, all the isomers indicated by theory have not proved capable of isolation. Corresponding to fumaric and maleic acids there should be geometrical isomers of all compounds of the same type, such as dichlorethylene, dimethylethylene, and the like, but as yet these compounds are known only in one form:—



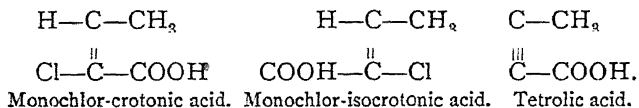
<sup>1</sup> *J. Chem. Soc. Abstracts*, 1891, ix. 1338. Cf. also A. W. Stewart, *Stereochemistry*, pp. 188-194.

In the case of dichlorethylene it is probable that the great attraction of chlorine for hydrogen is sufficient to cause the *cis* form to change spontaneously into the more stable *trans* modification; two isomers of the corresponding di-iodoethylenes ( $C_2H_2I_2$ ) have been isolated which probably correspond to the *cis* and *trans* forms.<sup>1</sup> The methyl group has no pronounced electro-positive or electro-negative character, and there is every reason to suppose that the two isomeric dimethylethylenes will be found capable of existence.

The crotonic acids stand midway between the dimethylethylenes on the one hand and maleïc and fumaric acid on the other. Their isomerism, as already explained,<sup>2</sup> cannot be due to structural differences, and is most satisfactorily expressed by the following stereochemical formulæ:—



The *cis* formula is assigned to solid crotonic acid because its monochlor-substitution product, in which the hydrogen and chlorine are adjacent, when treated with alcoholic potassium hydroxide readily loses a molecule of hydrochloric acid to form a doubly-unsaturated acid, tetrolic acid, whilst the corresponding iso-crotonic acid derivative forms tetrolic acid far less readily. The basis for thus assigning the configuration to such geometrical isomers is shown in the following projected space-formulæ<sup>3</sup>:—



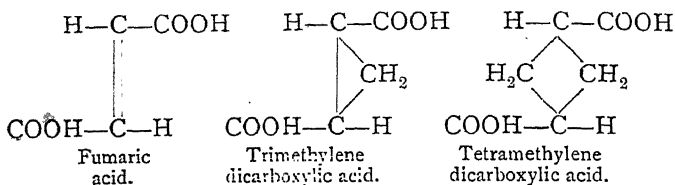
Amongst saturated cyclic compounds, such as trimethylene, many instances of geometrical isomerism are known; their conception and preparation has been a direct outcome of the work of van't Hoff and Wislicenus. It will

<sup>1</sup> Keiser, *J. Chem. Soc. Abstracts*, 1899, lxxvi. 398.

<sup>2</sup> Chap. viii, p. 149.

<sup>3</sup> For the most recent work on the chemistry of the Crotonic acids, cf. Autenrieth, *Berichte*, 1905, xxxviii. 2534.

readily be seen that dicarboxylic acids of the polymethylenes can give rise to geometrical isomers corresponding to maleic and fumaric acid, which are the dicarboxylic acids derived from ethylene. Thus, the analogues of fumaric acid will be as follows:—

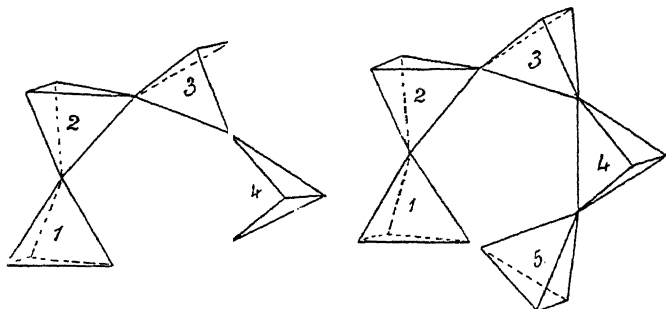


The geometrical isomerism of the hexamethylene carboxylic acids, the reduction products of the phthalic acids, has been most completely studied by von Baeyer. Attempts to extend these views to unsaturated cyclic compounds such as benzene and its derivatives have confirmed the structural symmetry of the benzene ring, but the indicated possibility of asymmetric molecules amongst simple benzenoid compounds, derived from three-dimensional formulæ, has, despite specific experiments for their preparation, not been realised. As yet all that is known of benzene is consistent with the view that the centres of gravity of all the atoms of the molecule lie in one plane.<sup>1</sup>

*Stereochemical Considerations regarding the Formation of Cyclic Compounds.*—Stereochemistry has not only played its part in unravelling the complexities of isomerism, but in another direction the conception of the tetrahedron has materially aided the advance of organic chemistry. The direction of the affinities of the carbon atom being indicated by the axes of the tetrahedron drawn from the centre to the solid angles, it follows that if several carbon atoms are united together in a chain they will not form a straight line, as would appear from the ordinary method of formulating such compounds, but will form a series of angles with each other, each equal to the angle subtended at the centre of a tetrahedron by one of its edges—viz., approximately  $109^\circ$ . This angle is such that if five carbon atoms be joined together they will almost form a regular pentagon, the valencies of the two end carbon atoms

<sup>1</sup> Cf. Stewart, *Stereochemistry*, chap. v. p. 502.

being, in fact, almost in the same straight line. Wislicenus pointed out that this fact offers a ready explanation of the tendency of chains of four or five carbon atoms to form a closed ring. The following figures illustrate this geometrical relation:—



*Representation of the combination of four and five carbon atoms according to the tetrahedron symbol for carbon.*

The formation of the anhydride of succinic acid is a simple illustration of this stereochemical relation. Succinic acid,  $C_2H_4(COOH)_2$ , contains a four carbon atom chain, and therefore the proximity of the carboxyl groups allows of the ready formation of an anhydride, whilst the space formulæ for its lower homologues, oxalic and malonic acids, do not indicate the likelihood of the formation of such closed chains, and as a matter of fact none are known. As stated above, the succinic acid must take up its least favoured configuration to form the anhydride and similar closed chain compounds.

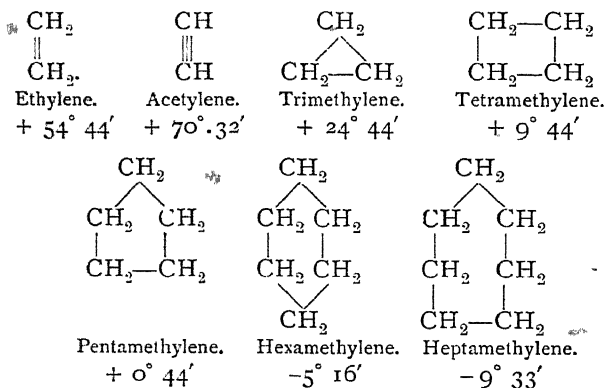
The preferential formation of anhydrides (lactones) from  $\gamma$ - and  $\delta$ -hydroxy-acids is also well explained from a stereochemical standpoint; these acids contain chains of four and five carbon atoms respectively.<sup>1</sup>

Similarly the formation of cyclic compounds and their relative stability must be dependent upon stereochemical considerations, a view which led von Baeyer to his important *Tension Theory* of cyclic compounds.<sup>2</sup> This theory

<sup>1</sup> Cf. Chap. viii., p. 157.

<sup>2</sup> *Berichte*, 1885, xviii., 2277; and 1890, xxiii. 1275.

he propounded from the fundamental consideration that "the formation of closed chains is obviously the phenomenon which can throw most light on the spatial arrangement of atoms. If a five- or six-membered chain closes easily with the formation of a ring, whilst one with more or fewer members does so only with difficulty or not at all, there must be definite spatial reasons for this difference." The theory also indicated a new reason for the recognised instability of unsaturated compounds such as ethylene and acetylene;<sup>1</sup> ethylene may, in fact, be looked upon as a two-membered carbon ring. The four affinities of the carbon atom as represented by the tetrahedron symbol form an angle of  $109^{\circ} 28'$  with each other. If two carbon atoms are united by a single bond the directions of the two affinities which link the two portions of the molecule fall naturally into line, but this must cease to be the case in the multiple linking of carbon atoms or in the formation of cyclic compounds. The direction of the valencies must then be deflected from their normal position, with the result that a condition of strain must arise proportional to the extent of the deviation. Regarding the carbon atoms in all such compounds as situated in one plane, the extent to which the affinity of each carbon atom is deflected from its normal direction in the various unsaturated and cyclic compounds can be calculated, with the following results:—



<sup>1</sup> Cf. Chap. iv. p. 52.

The figures lead in the first place to an accurate conception of a fundamental difference between single and double linking; further, to a good reason for the instability of unsaturated hydrocarbons, especially such as contain a triple link. This condition of strain in acetylene and its derivatives is a factor of importance in regard to their explosibility.<sup>1</sup> The tension in such compounds is at once relieved in the formation of addition products, which is their special characteristic, and the relative ease with which the latter result receives a very plausible explanation from these considerations.

Turning to cyclic compounds, a closed chain of five carbon atoms should form most readily and be most stable; with three or four carbon atoms the tension is greater, with six or seven it changes its sign. The relative stability of these cyclic compounds is fairly, but not fully, expressed by these figures. Hexamethylene rings are in general the most stable of the cyclic combinations, being in almost all cases even more readily formed and more stable than pentamethylene rings, as shown by thermochemical data,<sup>2</sup> but if it be taken into account that like atoms have in general a certain repulsion for one another, it is not difficult to understand the relatively greater stability of the six-membered rings. Experiments on the velocity of ring-formation, however, point to a greater stability of five-membered rings.<sup>3</sup> As the number of carbon atoms in a ring increases beyond six the tension and instability will increase too; hence, seven-membered rings are less stable than six-membered, and octamethylene rings are formed only with difficulty. Nine-membered carbon rings have not as yet been prepared, and it is doubtful whether they are capable of existence.<sup>4</sup>

The marked stability of the six-carbon-atom nucleus of benzene is not explained by the tension theory; as yet its applications are limited to saturated cyclic compounds.

Another form of intramolecular strain which has been already referred to is the "steric hindrance" to chemical

<sup>1</sup> Cf. Chap. iv. p. 47.

<sup>2</sup> Stohmann, *Berichte*, 1892, xxv. (Abstracts), 496.

<sup>3</sup> Menshutkin, *J. Chem. Soc.*, 1906, lxxxix. 1532; Hollemann and Voerman, *Chem. Centr.*, 1904, ii. 787.

<sup>4</sup> Cf. Chap. v. p. 60.



reactions which is caused by the presence of certain groups.<sup>1</sup> The numerous data which have been accumulated on this subject will doubtless be of assistance in elucidating the spatial arrangement of the atoms in the molecules of organic compounds.

In concluding this review of the deductions that have followed from the stereochemical theory of the carbon atom, the relation of optical activity to the origin of petroleum may be mentioned. In considering the evidence in favour of the vital origin of petroleum Walden has pointed out that the fact that optically active hydrocarbons occur in petroleum is a proof that it must have been formed by the decomposition of animal or vegetable products, especially the latter; such products would, in many cases, contain optically active constituents, and thus give rise to optically active hydrocarbons. The decomposition of carbides, on the other hand, would not result in the formation of optically active hydrocarbons.<sup>2</sup> This view has recently received interesting support from the discovery by Lewkowitsch<sup>3</sup> that optically active hydrocarbons can be produced by distilling glycerides of optically active fatty acids in presence of zinc dust.

*Asymmetric Optically Active Compounds of Silicon, Tin, Sulphur, and Selenium.*<sup>4</sup>—Carbon is the initial element in the fourth group of the periodic classification. All the elements of the group—carbon, silicon, germanium, tin, lead, titanium, zirconium, and thorium—are quadrivalent, and their compounds show many similarities to those of carbon in their properties and general chemical behaviour. It is, therefore, a matter of very great interest that the existence of optically active compounds of two of these elements, tin and silicon, has been established. The discovery of the active tin compounds is due to Pope and Peachey,<sup>5</sup> who succeeded in preparing the first compound

<sup>1</sup> Cf. Chap. viii. p. 159.

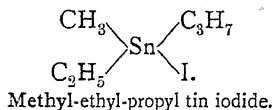
<sup>2</sup> Cf. Chap. vii. p. 106.

<sup>3</sup> *Berichte*, 1907, xl. 4161.

<sup>4</sup> Cf. A. W. Stewart, *Stereochemistry*, pp. 115-120. Also "Die optisch aktiven Verbindungen des Schwefels, Selens, Zinns, Siliziums und Stickstoffs," by M. Scholtz; *Sammlung chem. und chem. technischer Vorträge*.

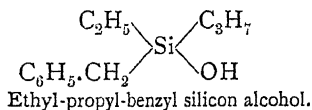
<sup>5</sup> *Proc. Chem. Soc.*, 1900, pp. 42 and 116.

of tin in which the metal is linked to four different groups, viz.:—methyl-ethyl-propyl tin iodide:—



By acting on this iodide with the silver salt of the dextro-rotatory camphor sulphonic acid referred to above, methyl-ethyl-propyl tin dextro-camphor sulphonate is obtained, which on evaporation of its aqueous solution separates the dextro-rotatory enantiomorph. This resolution of the initially formed racemic combination is very remarkable. It is due to the slight solubility of the dextro-salt, combined with the fact that the lævo-salt left after the initial separation of its antipode racemises as evaporation proceeds; the less soluble dextro-salt again separates, and this continues until all the water has been expelled. The proof of the existence of optically active, enantiomorphously related tin compounds leads to the tetrahedron symbol as the representation of the space configuration for all quadrivalent tin compounds.

The isolation of optically active silicon compounds has recently been achieved by Kipping,<sup>1</sup> who has prepared an asymmetric silicon derivative with the help of the Grignard reaction,<sup>2</sup> namely, the disulphonic acid of ethyl-propyl-benzyl silicon alcohol:—



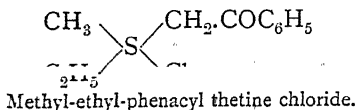
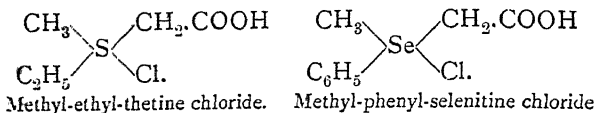
This acid was combined with an optically active base, methyl-hydrindamine, and on crystallisation a dextro- and a lævo-compound were isolated. Asymmetry is, therefore, no longer a characteristic of carbon alone, and there is no reason why compounds of other elements of group IV. of the periodic classification, such as lead, should not also show enantiomorphous relations.

The interest associated with the discovery of asymmetric

<sup>1</sup> *J. Chem. Soc.*, 1907, xci. 209; 1908, xciii. 198, 439, 457.

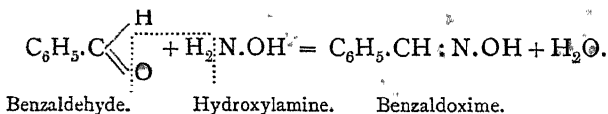
<sup>2</sup> *Cf. Chap. xi. p. 253.*

optically active compounds of sulphur<sup>1</sup> and selenium<sup>2</sup> is equally great. Here again a quadrivalent atom is attached to four different groups, to form an asymmetric molecule:—



Dextro- and lævo-rotatory derivatives of these compounds have been isolated from the initially formed, externally compensated combinations, in a similar manner to that adopted in the case of the tin compounds. The existence of enantiomorphously related compounds of sulphur and selenium points also to the acceptance of the tetrahedron as the symbol for the configuration of these elements, in those compounds in which they function as quadrivalent atoms; the sulphur or selenium is to be regarded as situated in the centre of the tetrahedron just as with carbon, their four affinities being directed towards the four solid angles.

*The Stereochemistry of Nitrogen.*<sup>3</sup>—In 1882 Victor Meyer discovered a general reaction for aldehydes and ketones, which has led to an important development of stereochemistry. He found that these substances react with hydroxylamine, a molecule of water being eliminated in the combination. In the case of benzaldehyde, for instance, the reaction takes place as follows:—



<sup>1</sup> Pope and Peachey, *J. Chem. Soc.*, 1900, lxxvii. 1072. Smiles, *J. Chem. Soc.*, 1900, lxxvii. 1174; and 1905, lxxxvii. 450.

<sup>2</sup> Pope and Neville, *J. Chem. Soc.*, 1902, lxxxi. 1552.

<sup>3</sup> A review of this subject is given in the *British Association Reports*, 1904, p. 160, "The Stereochemistry of Nitrogen," by H. O. Jones. Cf. also Scholtz, *loc. cit.*

The resulting compounds called *oximes*, some of which are liquids, others solids, are easily separated, and often serve for the isolation and especially for the identification of aldehydes and ketones.<sup>1</sup> A few years later (1887) Beckmann prepared an isomer of this benzaldoxime, whilst meanwhile unexpected conditions of isomerism had been observed amongst the oximes of a somewhat more complex compound, benzil. At first, attempts were made to account for the existence of these isomers by a difference in the linking of the constituent atoms and the experimental results, though certainly very puzzling, were somewhat favourable to this view. But the ease with which they changed into each other was inconsistent with this idea, and the analogy of such changes to those observed amongst stereochemical isomers led to an attempt to explain the isomerism of the benzil oximes by reference to the stereochemical relations of two of the contained carbon atoms. This view, however, had to be abandoned because it only gave a partial explanation of the facts, and led to erroneous conclusions in the case of closely allied substances.

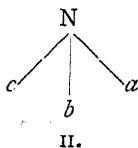
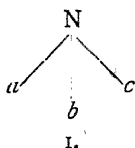
The more the experimental investigation of this group of compounds was pursued, the more involved did the isomeric relations become, until in 1890 Hantzsch and Werner<sup>2</sup> suggested a solution of the problem which has, as yet, proved thoroughly satisfactory. This solution is to be regarded as a development of the van't Hoff-Wislicenus stereochemical theory, applied to the nitrogen atom. Nitrogen is trivalent in ammonia and many other simple derivatives. In such compounds the direction of the three valencies of the nitrogen atom are most probably symmetrically situated and in the same plane as the centre of gravity of the nitrogen atom itself; otherwise, two isomeric compounds of the type *N.a.b.c.* should exist, related to each other in the same way as molecules containing an asymmetric carbon atom. Such a relation is shown in the following projection formulæ, but all attempts to prepare asymmetric trivalent nitrogen compounds have been unsuccessful<sup>3</sup>:—

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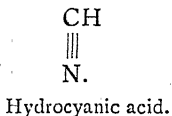
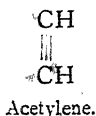
<sup>1</sup> Cf. Chap. xi. p. 261.

<sup>2</sup> "Räumliche Anordnung in Stickstoffhaltigen Moleculen," *Berichte*, 1890, xxiii. 11.

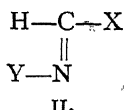
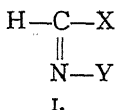
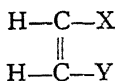
<sup>3</sup> Cf. Kipping and Salway, *J. Chem. Soc.*, 1904, lxxxv. 438.



In certain compounds, however, the direction of these affinities must be deviated from their normal position, on the basis of the stereochemical theory of the carbon atom, because many instances of nitrogen compounds are known in which the nitrogen atom takes the place of the trivalent group, CH, in a corresponding carbon compound. The simplest example of this is seen in the relation of acetylene to hydrocyanic acid:—

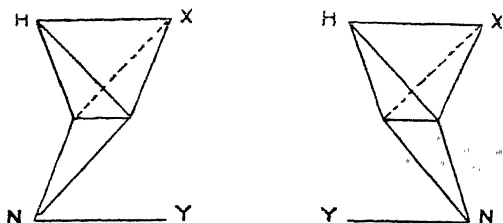


It is still more evident in cyclic compounds, such as pyridine and quinoline. In such cases geometrical isomerism is as fully precluded as in the case of acetylene itself. But the extension of this comparison to doubly-linked carbon atoms leads to the indication of geometrical isomers, in which the stereochemical differences are dependent upon the nitrogen atom, the substituent of the CH group. If, for instance, in a compound  $\text{X}-\text{CH}=\text{CH}-\text{Y}$ , one CH group be replaced by nitrogen to form  $\text{X}-\text{CH}=\text{N}-\text{Y}$ , then a stereochemical difference arises, which may be represented in the plane of the paper thus:—

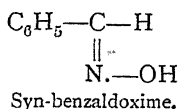
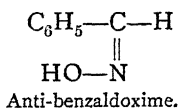


This idea was expressed by Hantzsch and Werner as follows:—"In certain compounds the three valencies of the nitrogen atom are directed towards the angles of a tetrahedron (of course, irregular), the fourth angle of which is occupied by the nitrogen atom itself." A representation

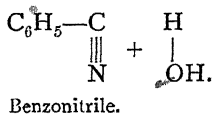
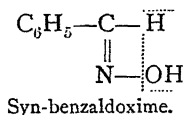
of this view, as shown on the models, which here again materially simplify the study of the subject, takes the following form for compounds of the type given above:—



The existence of two oximes of benzaldehyde is readily accounted for from this standpoint:—



the prefixes *syn* and *anti* being used to indicate this stereochemical difference. The ordinary and first known form of the oxime of benzaldehyde is a strongly refractive liquid, which can be crystallised by cooling, and then melts at 34°. The isomeric compound melts at a much higher temperature, 128°-130°; when heated it changes into the liquid form, and this also occurs on allowing its alcoholic solution to stand at the ordinary temperature. In assigning the relative configuration to these isomers, the greater stability of the compound of low melting point indicates that it is most probably the anti-modification, and this is confirmed by the fact that the less stable (labile) isomer very readily parts with a molecule of water to form benzonitrile, thus:—

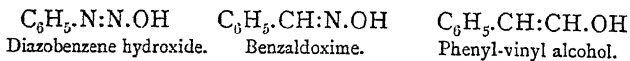


Other considerations confirm these configurations.

Compounds containing two carbonyl groups, such as benzil, can give rise to double oximes, or dioximes, and

the theory of Hantzsch and Werner indicates the possibility of three stereochemical isomers amongst such compounds. In the case of benzil all three are actually known, and their configuration, which is in accord with their relative stability, has been allotted by somewhat complex but quite satisfactory methods.

Although all the isomers indicated by the Hantzsch-Werner theory have not proved capable of isolation, the theory itself has proved a fruitful and successful incentive in the study of organic compounds, and, despite a considerable amount of controversy and opposition, may be regarded as generally accepted in so far as it relates to the oximes. Amongst other analogous groups of compounds similar stereochemical relations have naturally been looked for, and in many instances successfully. This has been especially the case in the diazo-group, in which many remarkable and involved isomeric relations are known; some of these are explained by structural isomerism,<sup>1</sup> but others can only be satisfactorily accounted for by the Hantzsch-Werner hypothesis of the stereochemical relations of the contained nitrogen atoms. The analogy between the diazo-compounds, the oximes and the derivatives of ethylene, substances which thus show similar conditions of geometrical isomerism, is seen in the following formulæ:—



As can be easily understood, stereochemical isomerism may offer a tempting haven of rest to the investigator, and for this very reason more care than ever is necessary to-day in deciding the method of linking of the atoms in a molecule. The newer theories of stereochemical isomerism have given an immense impetus to all inquiries regarding the structure of compounds, but they involve corresponding responsibilities which must not be overlooked.

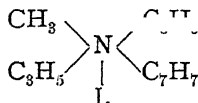
*Asymmetric Optically Active Nitrogen Compounds.*—When a tervalent nitrogen atom becomes quinquivalent, as in the formation of ammonium and organic ammonium compounds,<sup>2</sup> there is good reason to believe that this change of valency is accompanied by a change in the

<sup>1</sup> Cf. Chap. x. p. 211.

<sup>2</sup> Cf. Chap. x. p. 202.

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valency directions of the atom. This view applies also to the passage of divalent tin, sulphur and selenium to quadrivalent combination, and it is supported by the discovery that when five different substituting groups are attached to an atom of nitrogen, the compounds show asymmetric relations similar to those observed with compounds containing an asymmetric carbon atom. Nitrogen compounds of this type have been known for some time, but attempts to resolve them by means of acids, such as tartaric or camphoric, were unsuccessful. By the action of ferments, Le Bel succeeded, in 1891, in effecting a partial separation of methyl-ethyl-propyl-butyl ammonium chloride into its optical antipodes,<sup>1</sup> but the optical activity was so slight that the result did not meet with general acceptance. By the application of dextro-camphor sulphonic acid, however, the resolution of methyl-allyl-phenyl-benzyl-ammonium iodide,<sup>2</sup> and subsequently of other similarly constituted compounds<sup>3</sup> has been effected:—



Methyl-allyl-phenyl-benzyl-ammonium iodide.

By treating this iodide, which is, of course, obtained initially in an inactive form, with the silver salt of dextro-camphor sulphonic acid, the *d*-B.*d*.A and *l*-B.*d*.A compounds are got, which can be separated by fractional crystallisation from a suitable solvent and then converted into the respective iodides, *d*-B and *l*-B. These and other salts of this quarternary nitrogen base are optically active, and show the antipodal relations of compounds containing an asymmetric carbon atom, both in respect to their action on polarised light and in their crystallographic relations. The inactive combination is, however, not a racemic compound, but either a mechanical or pseudo-racemic mixture of the two component salts.

<sup>1</sup> *Comptes. rend.*, 1891, cxii, 724; 1899, cxxix. 548. *Berichte*, 1900, xxxiii. 1003.

<sup>2</sup> Pope and Peachey, *J. Chem. Soc.*, 1899. lxxv. 1127; Pope and Harvey, *J. Chem. Soc.*, 1901, lxxix. 828.

<sup>3</sup> Cf. H. O. Jones, *J. Chem. Soc.*, 1904, lxxxv. 223; and 1905, lxxxvi. 135.



## MODERN ORGANIC CHEMISTRY.

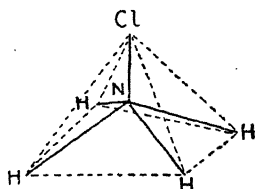
This important discovery of asymmetric quinquivalent nitrogen compounds proves that the valencies of the contained nitrogen atom cannot lie in one plane. A number of stereochemical configurations have been suggested to represent quinquivalent nitrogen, but none of these can, as yet, be accepted with anything approaching the confidence that is given to the tetrahedron symbol for carbon. Apart from the optically active nitrogen compounds referred to above, several instances of isomerism at other nitrogen compounds are known which to be best accounted for on the basis of stereoisomerism,<sup>1</sup> but much further investigation is necessary before the full story of the stereochemistry of nitrogen is determined. Meanwhile, some of the fundamental conditions that must be satisfied by any configuration for the nitrogen atom may be stated. No quinquivalent nitrogen compound is known containing either five hydrogen atoms or five alkyl radicals; at least one halogen atom or other electro-negative group is always present in such compounds, as shown in the following examples:—

$\text{NH}_4\text{Cl}$ .	<i>Ammonium chloride.</i>
$\text{N}(\text{CH}_3)_4\text{Cl}$ .	<i>Tetramethyl-ammonium chloride.</i>
$\text{C}_6\text{H}_5\cdot\text{NH}_3\text{Cl}$ .	<i>Phenyl-ammonium chloride.</i>
$\text{C}_6\text{H}_5\cdot\text{N}_3\text{Cl}$ .	<i>Phenyl-diazonium chloride.</i>

This experimental observation is consistent with the fact that five equivalent points cannot be symmetrically arranged around one point, and must be satisfied by any space formula for quinquivalent nitrogen. It is also necessary to account for the existence and formation of the asymmetric isomers. Of the various formulæ that have been proposed the *pyramidal* configuration suggested by Bischoff<sup>2</sup> appears to be the most satisfactory. The nitrogen atom is regarded as situated in the centre of a pyramid on a square base, the five solid angles of which are occupied by the elements or radicals with which it is in combination; of these angles, the apex is occupied by the electro-negative group (Cl. Br., etc.):—

<sup>1</sup> Cf. H. O. Jones, *British Association Reports*, 1904, p. 160.

<sup>2</sup> *Berichte*, 1890, xxiii. 1792.



Pyramidal formula for quinquevalent nitrogen compounds.

This representation, aided by some assumptions as to the mode of formation of quinquevalent from tervalent nitrogen compounds, can account for all the isomeric relations that have hitherto been observed, but it also provides for other possible isomers that are as yet unknown.<sup>1</sup>

Nitrogen heads the fifth group of the periodic system, and it is not unnatural therefore to look forward to the discovery of optically active molecules amongst the compounds of the remaining elements of the group, more especially amongst those of phosphorus and arsenic.

The elucidation of the atomic structure of compounds from definite stereochemical considerations, which began in 1874, was restricted to carbon compounds until 1890. This method of study has since been successfully extended to the compounds of nitrogen, silicon, tin, sulphur, and selenium, and there is little doubt but that it will throw light on the structure of the compounds of many other elements in the near future. Additions to the methods for the recognition of asymmetry and for the differentiation of stereo-isomers will constitute the greatest aid in the further investigation of stereochemical isomerism.

<sup>1</sup> Cf. H. O. Jones, *British Association Reports*, loc. cit. ; and *J. Chem. Soc.*, 1905, lxxxvii. 1721.

## CHAPTER XIII.

### THE SUGARS.

*The Carbohydrates.*

*The Chemical nature and Reactions of the Sugars.*—Division into aldoses and ketoses—The action of phenyl hydrazine upon aldoses and ketoses.

*The Synthetical preparation of Sugars.*

*The Stereochemistry of the Sugars.*—The relation of the configuration of sugars to the action of ferments.

*The Di-hexoses.*—Saccharose, lactose, and maltose; their relation to the hexoses.

*The Building up of Carbohydrates in plant cells.*

THE term "sugars" was originally applied to a number of naturally-occurring organic compounds which contained six or a multiple of six carbon atoms, and which were characterised by such properties as sweetness, carbonisation upon heating with the formation of "caramel," optical activity, and the capacity of being decomposed by ferments, such as yeast, with the formation of alcohol and carbonic acid. These characteristics as typified in the best-known members of the group—grape sugar, fruit sugar, cane sugar, and milk sugar—were regarded as the criteria for the inclusion of compounds in the sugar group.

The group was further recognised as a member of the division of organic compounds known as the *Carbohydrates*, a division which included, in addition to the sugars, starch, cellulose, and gums. Their generic name was derived from the fact that they are compounds of carbon, hydrogen, and oxygen, in which the two last elements are present in the same proportion as in water; they have the general formula  $C_mH_{2n}O_n$ . The term carbohydrates, although still retained to include the above groups of compounds, lacks accuracy in being both too general and too exclusive. Compounds are known having the empirical composition

## THE SUGARS.

of the carbohydrates which are quite distinct in their chemical character, whilst others, which have not this empirical composition, should be included in virtue of their structure and reactions.

A more accurate classification of the group of carbohydrates has been necessitated by the great additions that have been made to the scope of the sugar group. These additions have consisted chiefly in the preparation of compounds by synthetical methods, which have served to determine the structure and the full genetic relations of the simpler sugars. While some of these possess, to a greater or less extent, the characteristic properties of the naturally occurring sugars, and are similar in their chemical structure, others are quite distinct in their chemical nature, but closely related on account of the reactions, by means of which they can be converted into or obtained from the former. The sugar group must now be regarded as including all these compounds.

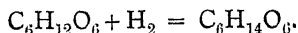
In respect to the other members of the carbohydrate group, the starches, cellulose, and gums, comparatively little is known of their structure or of their exact place in the division of organic compounds. They are amorphous products of high molecular weight, closely related to the sugars, into which many of them can be converted both by the action of ferments and by chemical agencies. They have been the subject of many important investigations, but as yet these studies, apart from those of a technical bearing, have been chiefly concerned with their relations to the simpler sugars. Now that the knowledge of the latter is well developed, that of these more complex carbohydrates is likely to be successfully extended.

The present knowledge of the structure of the sugars is chiefly due to the epoch-making researches of Emil Fischer, which were commenced some twenty years ago. Up to that time only six of the simpler sugars were known, all products from either the animal or the vegetable kingdom; now no fewer than fifty-two have been identified, of which seven are natural products.

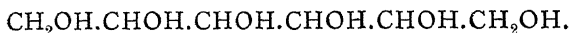
In order to give a review of the present knowledge of the sugar group, without entering into details of the characteristics of the individual members, the general chemical nature and reactions of the sugars will be first considered;

this will be followed by some account of the synthetical methods for their preparation and an outline of their stereochemical relations. The chapter will conclude with a reference to the building up of carbohydrates in the cells of plants.<sup>1</sup>

*The Chemical Nature and Reactions of the Sugars. Division into Aldoses and Ketoses.*—The natural sugars, glucose or grape sugar, and fructose or fruit sugar, have both the molecular formula  $C_6H_{12}O_6$ . They can be converted into penta-acetyl compounds, and therefore contain five hydroxyl groups,<sup>2</sup> each of which has been satisfactorily shown to be attached to a separate carbon atom in the molecule. Upon reduction they each take up two atoms of hydrogen to form a hexahydric alcohol according to the



The latter has been proved to be the hexahydroxy-derivative of normal hexane, and has the following structure:—



These reactions lead to two probable formulæ for glucose and fructose:—

- I.  $CH_2OH.CHOH.CHOH.CHOH.CHOH.CHO.$
- II.  $CH_2OH.CHOH.CHOH.CHOH.CO.CH_2OH.$

I. represents an aldehyde-alcohol, II. a ketone-alcohol; either would give a hexahydric alcohol upon reduction.<sup>3</sup>

These formulæ were not differentiated until Kiliani (1885-87) proved that glucose and fructose differed in their oxidation products, and in the compounds that result from the hydrolysis of their addition products with hydrocyanic acid.

The latter changes are the more instructive. Like all

<sup>1</sup> A full account of the sugars will be found in the following works:—

*Les Sucres et leurs principaux dérivés*, Maquenne, 1900.

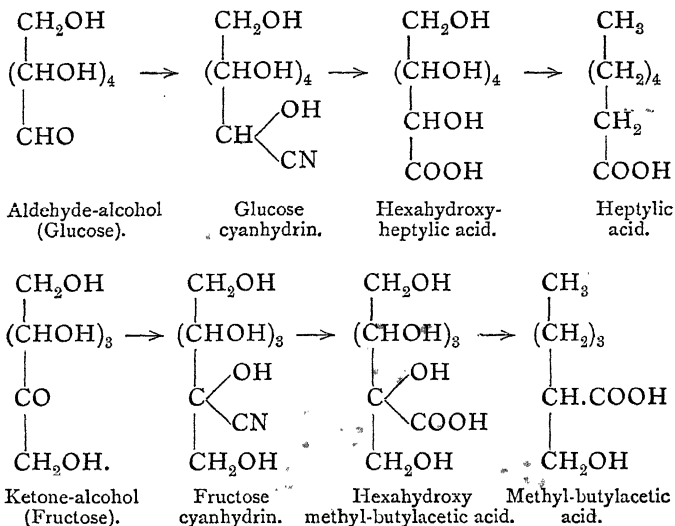
*Die Chemie der Zuckerarten*, Lippmann, 1895.

*Kurzes Handbuch der Kohlenhydrate*, Tollens, second edition, 1895,

<sup>2</sup> Cf. Chap. viii. p. 144.

<sup>3</sup> Cf. Chap. viii. p. 155.

aldehydes and ketones, these sugars form cyanhydrins, from which acids are obtained by the action of mineral acids or of alkalis.<sup>1</sup> The acids that result thus from glucose and fructose differ in their structure; that from the former is converted into normal heptylic acid by the reduction of the contained hydroxy-groups, whilst that from the latter yields an isomer, methyl-butylacetic acid. It was thus proved that both the above formulæ are represented in the sugar group; glucose is an aldehyde-alcohol, fructose a ketone-alcohol. These changes, which are represented in the following formulæ, prove in addition the presence and position of the aldehyde and ketone groups respectively in these two sugars:—



This differentiation, which is confirmed by other reactions, forms the basis for the classification of the whole of the sugar group. The termination "ose" has been chosen for the nomenclature of these compounds; the aldehyde-alcohols are called *aldoses*, the ketone-alcohols

<sup>1</sup> Cf. Chap. viii. p. 138.

*ketoses*. Since both glucose and fructose contain six carbon atoms, they are called an aldo-hexose and a keto-hexose respectively. The synthetical methods for the preparation of the sugars have led to the isolation of ketoses and of aldoses containing both more and fewer than six atoms of carbon; to all of these a similar nomenclature is now applied. A sugar containing two atoms of carbon is known as a "biose," one with three as a "triose," and so on.

This classification is exemplified in the following table:—

<i>Bioses.</i>	$\text{CH}_2\text{OH}.\text{CHO}.$	Aldose.	(Glycollic aldehyde)
<i>Trioses.</i>	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CHO}.$	Aldose.	(Glyceryl aldehyde)
		Ketose.	(Dihydroxy-acetone)
<i>Tetroses.</i>	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHO}.$	Aldose.	(Erythrose)
	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CO}.\text{CH}_2\text{OH}.$	Ketose.	(Erythrulose)
<i>Pentoses.</i>	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHO}.$	Aldose.	(Arabinose)
	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CO}.\text{CH}_2\text{OH}.$	Ketose.	(Arabinulose)
<i>Hexoses.</i>	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHO}.$	Aldose.	(Glucose)
	$\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CO}.\text{CH}_2\text{OH}.$	Ketose.	(Fructose)

All these compounds, with the exception of the biose, glycollic aldehyde, and the keto-triose, dihydroxy-acetone, contain one or more asymmetric carbon atoms, the aldose in each case containing one more such asymmetric atom than the corresponding ketose. Hence, stereochemical isomerism arises in this group, and these isomeric relations become more complex, of course, with an increase in the number of asymmetric groupings present in the molecule; in the hexose group sixteen stereochemically isomeric aldoses and eight ketoses are theoretically possible.

The hexoses are by far the most completely studied compounds of the sugar group, and all the important reactions of the sugars were first investigated with and applied to these compounds. It will suffice, now that the chemical nature of the simpler sugars has been explained, to consider their further reactions in respect to the typical atomic groups of the aldoses and the ketoses, viz. :—



Aldose group.

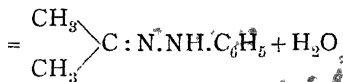
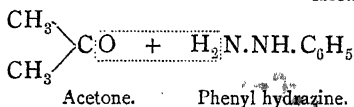
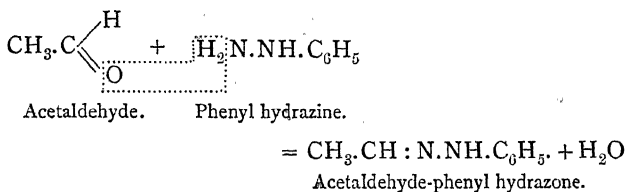


Ketose group.

Both aldoses and ketoses are very soluble in water, sparingly soluble in alcohol and insoluble in ether; their

solubility in water increases with the number of hydroxyl groups present in the molecule. Although fairly easily crystallised when pure, their crystallisation is greatly hindered by the presence of other products in their solutions, and consequently they are extremely difficult to isolate in a state of purity; also they are but weakly acidic in character, so that methods of isolation by means of metallic salts are but seldom available. This difficulty of separation and purification was for a long time the stumbling-block in their investigation. It was removed by Emil Fischer's discovery (1887) that almost all sugars form well-defined crystalline compounds with phenyl hydrazine, a discovery which marked the beginning of his investigations in this group.

*The Action of Phenyl Hydrazine upon Aldoses and Ketoses.*—Phenyl hydrazine is the phenyl derivative of hydrazine or diamide; it reacts with all aldehydes and ketones, on somewhat similar lines to hydroxylamine, to form stable and, usually, sparingly soluble compounds, called hydrazones.<sup>1</sup> The reactions with acetaldehyde and acetone are represented by the following equations:—



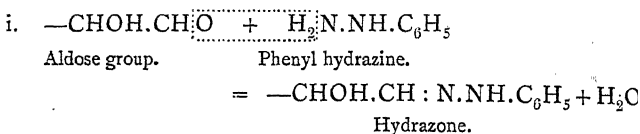
Aldoses and ketoses behave similarly, but most of the hydrazones formed are very soluble in water and difficult

<sup>1</sup> Cf. Chap. xi. p. 261.

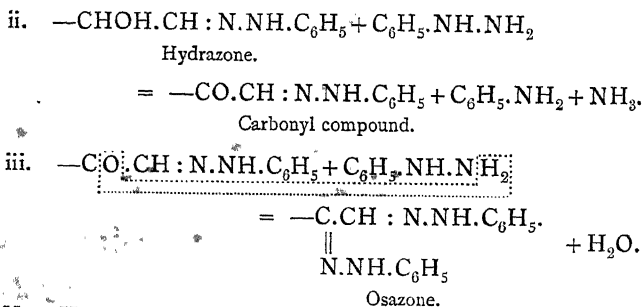


to crystallise; they offered, therefore, but little help in the study of the sugar group. Fischer found, however, that by further reaction with phenyl hydrazine the sugars formed sparingly soluble, crystalline compounds which were readily isolated, and it is these that have been of such value in the investigation of the group. They result by the action of a second molecule of phenyl hydrazine on the originally formed hydrazone. The change is somewhat complex, but has been satisfactorily proved to proceed on the following lines with the aldoses and ketoses respectively:—

### I. *Aldose.*



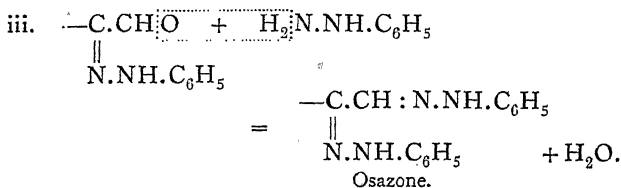
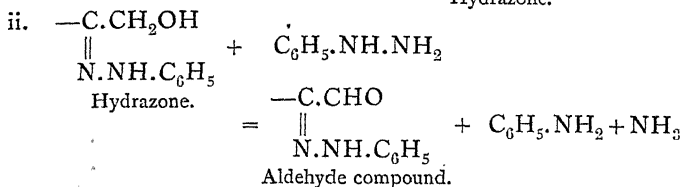
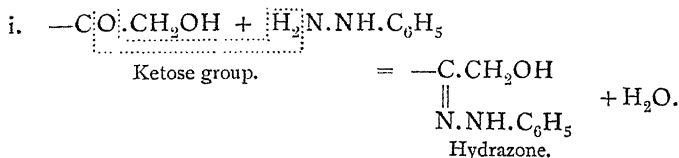
On warming the solution of the hydrazone thus formed with an excess of phenyl hydrazine the CH.OH group of the aldose is first oxidized to the CO group, the phenyl hydrazine being itself thereby reduced to aniline and ammonia; the phenyl hydrazine then reacts with the carbonyl group which has been formed, to produce a double hydrazone called an *osazone*.



### II. *Ketose.*

In the case of the ketoses the ketonic group first reacts to form a soluble hydrazone; the primary alcohol group of the ketose is next oxidised to the aldehyde group, which

then combines with the second molecule of phenyl hydrazine to form the osazone.

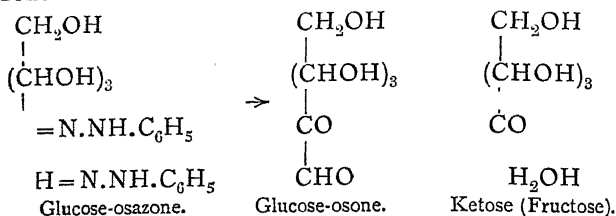


These osazones are the sparingly soluble, crystalline compounds which have served for the isolation of the sugars; by virtue of their characteristic melting points they are also of great service for the identification of the sugars.

It will be noted that in the above reactions the same formula results for both the osazone group of the aldose and for that of the ketose; the products obtained, if the rest of the molecules is alike, are really identical, a point of importance in respect to the relative configuration of the sugars. The difference between an aldose and a ketose may be restricted to the groups attached to the two end carbon atoms of the chain, a difference which is eliminated in the formation of the osazone.

The osazones are decomposed by strong hydrochloric acid with the elimination of the phenyl hydrazine groups and the formation of a ketone-aldehyde, called an *osone*; glucose-osazone, for instance, is thus converted into

glucose-osone. The osones can then be reduced to ketoses; they do not yield aldoses. The following formulæ represent these changes in the case of glucose-osazone:—

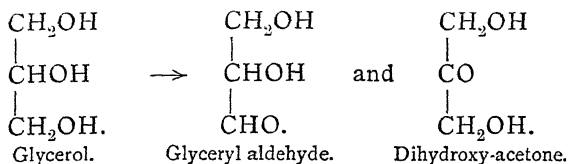


It is by these means that sugars can be obtained from their osones; also, that an aldose can be converted into a ketose *viâ* their common osazone. Fructose has been thus prepared from glucose, as represented in the above formulæ.

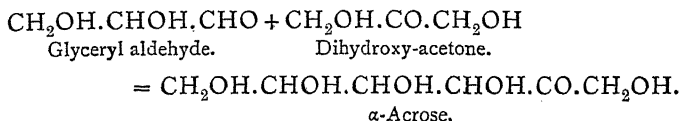
*The Synthetical preparation of Sugars.*—As long ago as 1861 Butlerow found that a product resembling sugar was formed by treating formaldehyde with lime-water; it was obtained as a sweet syrup, and was not acted on by yeast. A similar substance was subsequently (1886) obtained by Loew, also from formaldehyde, whilst Grimaux prepared a product which had the reducing and fermentative properties of the sugars by the oxidation of glycerol in presence of finely divided platinum (1887). This was all that preceded Fischer's investigations which date from 1887.

The first synthetical reaction employed by Fischer in the preparation of the sugars consisted in treating acrolein dibromide with sodium hydroxide; a fermentable syrup was formed which proved to be a mixture of two compounds, both isomeric with glucose, and to which he gave the names  $\alpha$ - and  $\beta$ -acrose. The former was found to be present in small quantity in the products obtained by Butlerow and by Loew from formaldehyde. The yield of these new compounds was extremely small and the initial material was not very accessible. The method was improved by starting from glycerol, which gives a similar mixture upon oxidation with bromine water in presence of alkali. The first oxidation product is known as

*glycerose*; it is a mixture of two compounds, glyceryl aldehyde and dihydroxy-acetone,<sup>1</sup> both members of the sugar group as trioses. This initial oxidation has already been referred to;<sup>2</sup> it is represented by the following formulæ:—

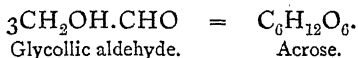


Under the influence of the alkali these two constituents of glycerose unite to form a hexose, which was isolated by means of its osazone, from which a ketose was obtained by subsequent decomposition and reduction by the method already explained. This ketose is  $\alpha$ -acrose. Its formation may be represented by the following equation:—



Acrose is optically inactive; upon reduction it behaves exactly like glucose and fructose, forming a hexahydric alcohol.

Although this synthesis starts from a readily accessible compound, the small yield of the sugar obtained (about 0.2 grams from 1 kilogram of glycerol) led Fischer to look for other methods of preparation. It is interesting, however, to note that the simplest member of the sugar group, glycollic aldehyde, the only biose possible, can be converted into a mixture of  $\alpha$ - and  $\beta$ -acrose by the prolonged action of dilute alkali at a low temperature,<sup>3</sup> a reaction involving the polymerisation of three molecules of the biose:—



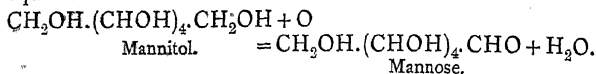
<sup>1</sup> According to Wohl (*Berichte*, 1900, xxxiii. 3095), glycerose consists almost entirely of dihydroxy-acetone.

<sup>2</sup> Cf. Chap. viii. p. 156.

<sup>3</sup> Fenton, *J. Chem. Soc.*, 1900, lxxvii. 129.

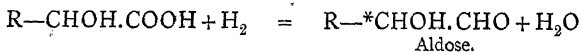
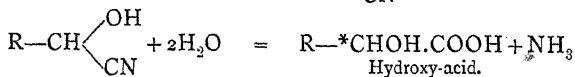
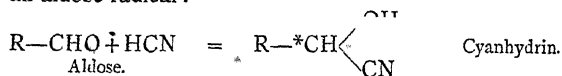
Glycollic aldehyde has also been found as an intermediate product in the synthesis of sugars from formaldehyde.<sup>1</sup>

The later synthetical reactions employed by Fischer are of an extremely simple character, but their realisation in the laboratory necessitated most careful and laborious work, especially in respect to the isolation and identification of the resulting products. These reactions, which are restricted to the preparation of aldoses, consist in the formation of aldehyde-alcohols, either by the oxidation of the corresponding alcohols or by the reduction of the corresponding acids. The oxidation method was first employed in the preparation of a new sugar *mannose*, by the action of dilute nitric acid on the hexahydric alcohol mannitol, which occurs in the dried sap of the manna ash (*Fraxinus ornus*); it takes place according to the equation:—



Mannose bears the closest possible resemblance to glucose in its chemical behaviour, solubility and power of undergoing fermentation with yeast; it is optically active, being derived from active mannitol, and its osazone is identical with that of glucose. Since its synthetical preparation, it has been obtained by the hydrolysis of the cellular tissue of many plants, such as the ivory-nut, the Norway spruce, and the white pine.

The reduction method involves the previous preparation of the acids which are accessible from other aldoses, either by Kiliani's reaction (p. 329) or by direct oxidation. The former gives a means for ascending the series of sugars, as expressed in the following equations, in which R represents an aldose radical:—



<sup>1</sup> Euler, *Berichte*, 1906, xxxix. 45.

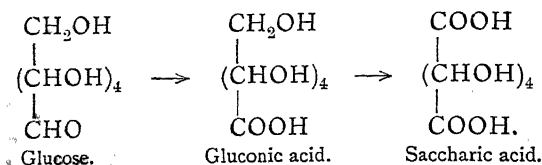
By this method pentoses have been converted into hexoses and the latter, successively, into sugars containing 7, 8 and 9 atoms of carbon, the heptoses, octoses, and nonoses. It is to be noted that in this reaction a new asymmetric carbon atom is introduced (marked with an asterisk) so that two new stereo-isomeric acids and aldehydes can, and generally do, result.

Thus, starting from arabinose, a readily accessible pentose which can be prepared from gum arabic, Fischer obtained two new sugars, a mannose and a glucose; the former differs from the mannose obtained by the oxidation of mannitol in its optical activity, and is known as *l-mannose*, the latter is *l-glucose*, and resembles ordinary grape sugar (*d-glucose*) in everything except its action on polarised light.<sup>1</sup> Four hexoses (*d-* and *l-glucose* and *d-* and *l-mannose*) were available for continuing this reaction to the preparation of heptoses, octoses and nonoses, several of which have been successfully isolated. Since two new sugars are possible at each stage, the number of compounds that might thus be prepared increases rapidly with the ascent of the series. The reaction is also applicable, of course, to the lower members of the sugar group, from the biose, glycollic aldehyde upwards, nor can any limitation be set to the length of the aldose chain that might thus be prepared. Little interest, however, centres in such extensions of a general reaction unless the new compounds have some direct bearing on theoretical or practical problems. The latter have not as yet come within the scope of the synthetical sugars; the former have been almost sufficiently exploited by Fischer's studies in the hexose group and its immediate homologues.

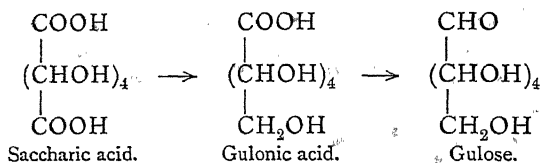
The preparation of the sugar acids by direct oxidation of aldoses and their subsequent reduction to new aldoses involves an interesting change dependent upon the asymmetry of the sugar molecule. When glucose, for instance, is oxidised, it first forms a monobasic acid, gluconic acid;

<sup>1</sup> The prefixes *d* and *l* do not refer to the actual direction in which the sugars rotate the plane of polarised light, but to their genetic relations. All compounds derived from ordinary glucose are prefixed *d*; its osazone and the derived ketose (ordinary fruit sugar) are known as *d-glucosazone* and *d-fructose*, although both are lævo-rotatory. In this connection compare Rosanoff, *J. Amer. Chem. Soc.*, 1906, xxviii. 114.

this is the characteristic change for any aldehyde upon oxidation. On further oxidation the primary alcohol group,  $\text{CH}_2\text{OH}$ , which is situated at the opposite end of the chain to the aldehyde group, is oxidised to carboxyl, and a dibasic acid, saccharic acid, results. These changes are represented by the following formulæ:—



When saccharic acid is reduced under suitable conditions, the above changes are reversed, in so far as a monobasic acid and an aldose are formed successively, but these are not identical with the previous compounds. The reduction takes place at the opposite end of the chain to that originally attacked; first a new acid, isomeric with gluconic acid and called gulonic acid, is formed, and then a new aldose, *gulose*, as follows:—



The difference between gluconic and gulonic acids, and similarly between glucose and gulose, will be apparent when the stereochemical relations of the aldoses of the hexose group are considered. By the application of this reaction to *d*- and *l*-glucose Fischer obtained *d*- and *l*-gulose.

With grape sugar (*d*-glucose) and arabinose as the starting-points, five new sugars were thus prepared. *Galactose*, the product of hydrolysis of milk-sugar and other carbohydrates, is also an aldo-hexose, so that together with *d*-glucose seven of the sixteen theoretically possible compounds of this group were accounted for. A further reaction of Fischer's added three more isomers.

When the oxidation product of glucose, gluconic acid,

is heated with a little pyridine or quinoline, it is partially converted into an isomeric acid, mannonic acid; the change, which is similar in character to the conversion of dextro- or lævo-tartaric acid into meso-tartaric acid by heating, is reversible, and mannonic acid can be similarly converted into gluconic acid. A new acid, idonic acid, can be similarly obtained from gulonic acid, and upon reduction it forms a new sugar, *idose*. Both *d*- and *l*-*idose* were thus prepared from *d*- and *l*-gulose, and a third additional sugar, *d*-*talose*, from *d*-galactose. Finally, *l*-galactose was prepared from *d*-galactose by a somewhat complex series of reactions, and converted by the above reaction into *l*-*talose*, thus bringing up the total number of sugars to twelve out of the sixteen possible isomers, viz.:—

<i>d</i> - and <i>l</i> -Glucose.	<i>d</i> - and <i>l</i> -Idose.
<i>d</i> - and <i>l</i> -Mannose.	<i>d</i> - and <i>l</i> -Galactose.
<i>d</i> - and <i>l</i> -Gulose.	<i>d</i> - and <i>l</i> -Talose.

The methods for obtaining the remaining four aldohexoses, and their relation to the other members of the group, are so clearly indicated by Fischer's work that their synthesis will doubtless follow on lines similar to those mentioned above. By the application of certain of the above reactions to the sugars containing five carbon atoms, the pentoses, Fischer has added two new sugars to this group.

In addition, Wohl,<sup>1</sup> and subsequently Ruff,<sup>2</sup> have discovered methods for descending the series of the sugars. Pentoses have thus been prepared from hexoses, and tetroses from pentoses; the knowledge of the aldo-pentose group, which includes eight members, is in fact fairly complete, six of them being known, of which two occur in Nature.

The ketoses, as already stated, can be obtained from the aldoses via their osazones. So far this reaction has only been applied to the preparation of *d*- and *l*-fructose, but three other keto-hexoses—*d*- and *l*-sorbose and *d*-tagatose—have been obtained by other means, so that five of the eight possible stereo-isomers are now known.

*The Stereochemistry of the Sugars.*—The laboratory in-

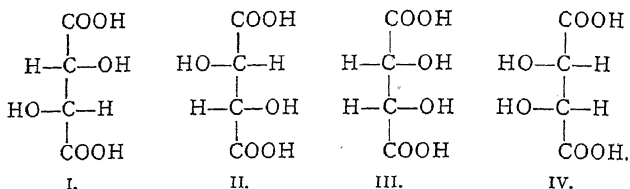
<sup>1</sup> *Berichte*, 1893, xxvi. 730; and 1899, cii. 3666.

<sup>2</sup> *Berichte*, 1899, xxxii. 550 and 3672.



vestigations of Emil Fischer, which have been the means of unravelling the complexities of the simpler sugars, find their complement in the insight displayed in assigning the stereochemical formula to each member of the group. It will be remembered that the isomerism of the sixteen aldo-hexoses is due to the spatial arrangement of the constituent atoms and radicals; it forms the most complete development of the theory of the asymmetric carbon atom. The method adopted to assign the correct configuration to each of these stereo-isomers is somewhat intricate, and can only be followed by means of a detailed study of the genetic relations of the compounds themselves and of many of their derivatives. It must suffice, therefore, to give an outline of the method employed.<sup>1</sup>

In a previous chapter<sup>2</sup> the following four, apparently different, projected stereochemical formulæ for tartaric acid were given, but it was shown that if properly interpreted III. and IV. are identical:—



This is always the case when the two halves of the molecule are similar, but if the substituents at the top and bottom of the chain are different the identity of the two forms disappears, and all four isomers are theoretically possible and different. For instance, if one carboxyl group

<sup>1</sup> Details will be found in resumé's given by Emil Fischer, *Berichte*, 1890, xxiii. 2114; and 1894, xxvii. 3189.

Also in the following books:—

*Stereochemistry*, Stewart, chap. iv.

*The Spirit of Organic Chemistry*, Lachmann, 1899.

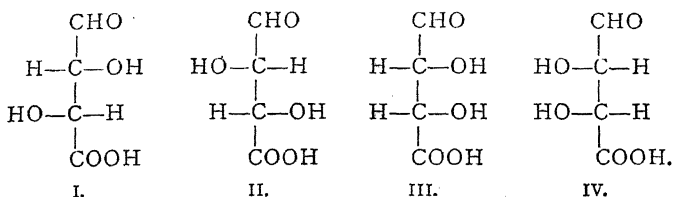
*Lehrbuch der organischen Chemie*, Meyer and Jacobsen, 1893; second edition, 1907.

*Grundriss der Stereochemie*, A. Hantzsch, second edition, 1904;

English translation of first edition, *The Elements of Stereochemistry*, C. G. L. Wolf, 1900.

<sup>2</sup> Chap. xii. p. 291.

in tartaric acid be replaced by an aldehyde group, the four configurations will be:—



Of these, I. and II. form an enantiomorphous pair, and can give rise to a racemic combination, as in the case of the tartaric acids; III. and IV. now also form an optically active, enantiomorphous pair, and can combine to form a second racemic modification. Their relative configuration can be, in part, decided by the study of their oxidation products. The corresponding aldehyde acids I and II. will each yield a different dibasic acid, whilst the acid obtained from III. and IV. will be the same. The stereochemical difference of the two latter compounds is therefore dependent upon the top and bottom difference in their respective molecules; it is removed when this difference is eliminated. This is one of the methods adopted to differentiate the configurations of stereochemical isomers.

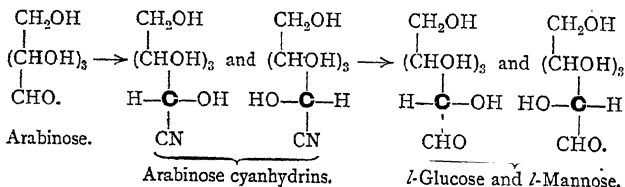
Turning now to compounds of the glucose group, they may be divided into two sections—the aldehyde alcohols (aldo-hexoses) and the monobasic acids obtained from them by oxidation, on the one hand, and the dibasic acids, such as saccharic acid, and the reduction products of the aldoses, the hexahydric alcohols, on the other. All these compounds contain four asymmetric carbon atoms, indicated by thick type in the formulæ given below; those in the first section show a similar top and bottom difference to the above aldehyde acids, whilst those in the second section are similarly constituted to the tartaric acids:—

- I.  $\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHO}.$  *Aldose.*  
 $\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{COOH}.$  *Monobasic acid.*
- II.  $\text{COOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{COOH}$  *Dibasic acid.*  
 $\text{CH}_2\text{OH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CHOH}.\text{CH}_2\text{OH}.$  *Hexahydric alcohol.*

Sixteen stereo-isomers of the first section are theoretically possible and ten of the second. The former comprise eight enantiomorphous pairs, all optically active, and therefore an additional eight racemic combinations are possible. The latter comprise two forms, which are inactive on account of internal compensation, and four enantiomorphous pairs. Of the two sections have been

II., upon oxidation. Their difference is, therefore, due solely to the asymmetry of the two ends of the chain. Further, this saccharic acid is optically active, so that two of the ten possible configurations for section II. are put out of court as possible formulæ for it.

Of other relations that have aided in determining the configuration of the aldo-hexoses, the cyanhydrin reaction of Kiliani and the formation of osazones are the most important. As stated, the cyanhydrin derived from arabinose gives both gluconic and mannonic acids on hydrolysis, from which *L*-glucose and *L*-mannose can be prepared. Their isomerism must obviously depend on the configuration of the substituents attached to the added asymmetric carbon atom, and these two sugars must differ, therefore, in the manner indicated by the following formulæ:—

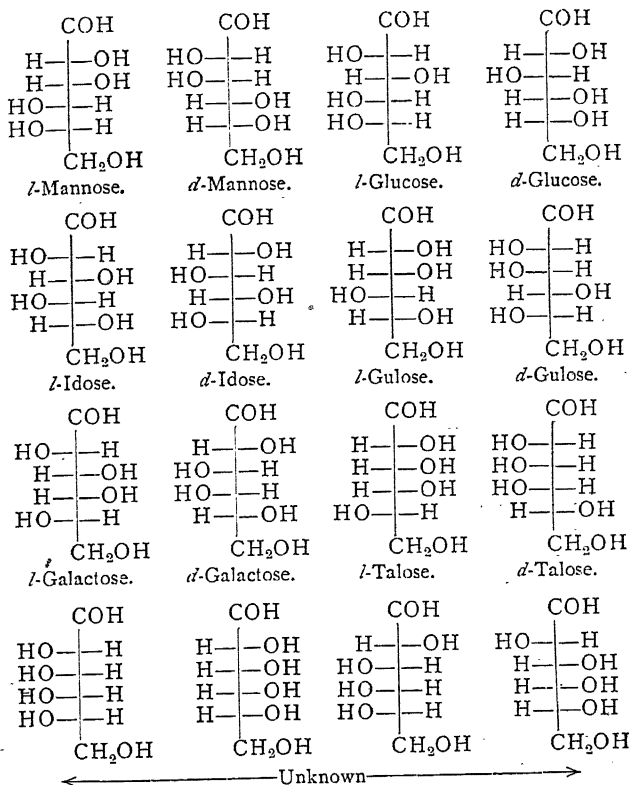


This relative configuration is confirmed by the fact that *L*-glucose and *L*-mannose form the same osazone; their difference is eliminated when the asymmetry of the carbon atom next to the aldehyde group is destroyed.

By a careful study of such relations as the above, Fischer has succeeded in determining the configurations of all the aldo-hexoses, and of many of the associated alcohols,

acids, and pentoses. In the following table the projected stereochemical formulæ of the aldo-hexoses are given. Of the sixteen isomers, four are unknown:—

*Stereochemical Formulæ of the Aldo-hexoses.*



*The Relation of the Configuration of the Sugars to the Action of Ferments.*<sup>1</sup>—In many of the reactions employed in the preparation of the synthetical sugars racemic combinations result, which can be resolved into the optical isomers

<sup>1</sup> Cf. J. W. Mellor, *Chemical Statics and Dynamics*, 1904, p. 361.

by the methods already described.<sup>1</sup> *a* Acrose, for instance, the first synthetically prepared sugar, is rapidly attacked by yeast, leaving *l*-fructose, the enantiomorph of ordinary fruit sugar; it is the racemic form of this keto-hexose. Partial fermentation is the only process for splitting such racemic combinations that has been applied to the sugars themselves, but their acids have been successfully resolved by the fractional crystallisation of suitable salts with asymmetric bases, such as strychnine and morphine. The application of fermentative action to the preparation of the sugars has been followed by the study of its relation to the configuration of the compounds of this group. The investigations of Fischer and Thierfelder,<sup>2</sup> and of E. F. Armstrong,<sup>3</sup> have established some important conclusions in respect to this relationship, which have an interesting bearing on the asymmetry of the products of animal and vegetable metabolism.

Two classes of ferments, formerly distinguished as "organised" and "unorganised" ferments, are known. The former includes such ferments as the yeasts, living organisms which effect chemical changes during the processes of their growth and reproduction; the latter, now generally classed as "enzymes," are complex products secreted by living organisms, which can be extracted by suitable means, and which resemble the proteins in their chemical character. Recent years have witnessed most important extensions of the knowledge of these ferments. A great variety of metabolic and other simpler chemical changes, most of which appear to be hydrolytic, are effected by enzymes, such as the hydrolysis of carbohydrates by maltase and invertase, and that of the glucosides by emulsin and myrosin; in addition, many changes, formerly attributed to organised ferments, are now known to be due to extractable enzymes, such as the zymase of alcoholic fermentation.<sup>4</sup>

<sup>1</sup> Chap. xii. p. 294.

<sup>2</sup> *Z. Physiolog. Chem.*, 1898, xxvi. 61.

<sup>3</sup> *Roy. Soc. Proc.*, 1904, lxxiii. 500, 516, and 526

<sup>4</sup> Literature on Fermentation:—

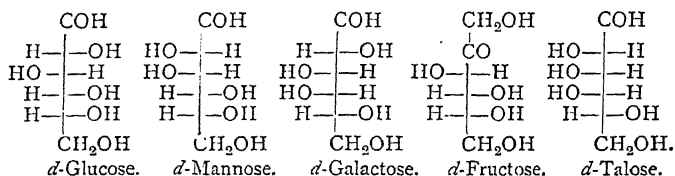
*The Soluble Ferments and Fermentation*, J. Reynolds Green, 1904.

*The Chemical Products resulting from Fermentations*, R. H. A. Plimmer, 1903.

*Ferments and their Actions*, Oppenheimer, trans. by Mitchell, 1901.

*The Natural History of Digestion*, chap. v., A. Lockhart Gillespie, Contemporary Science Series, 1898.

Both the organised ferments and the enzymes show remarkable selective power in their action on the sugars, a power which is not restricted to a discrimination between enantiomorphous forms as in Pasteur's method for the resolution of racemic combinations.<sup>1</sup> Fischer and Thierfelder studied the action of a variety of pure yeast cultures on the aldo-hexoses and found that of the twelve known compounds of this group only the three natural products, *d*-glucose, *d*-mannose, and *d*-galactose are decomposed, and of the keto-hexoses, only ordinary fruit sugar, *d*-fructose. In each case carbon dioxide and alcohol are formed; the rate of the decomposition is about the same for glucose, mannose and fructose, but galactose is more slowly attacked and certain species of yeast which ferment the other sugars are entirely without action upon it. A comparison of the configuration of these four sugars with that of *d*-talose, as an example of a non-fermentable aldo-hexose, shows how small a difference in the configuration of the molecule suffices to arrest the action:—



In glucose, mannose, and fructose the relative position of the hydrogen atoms and hydroxyl groups, round the three lower asymmetric carbon atoms, is the same; the two former differ only in respect to the grouping of these substituents round the top carbon atom. Galactose similarly differs from glucose in the disposition of the groups attached to one of its carbon atoms, whilst in the case of talose the groups attached to two of the asymmetric carbon atoms are differently disposed to their position in glucose. The difference in the configuration of galactose and glucose is associated with a difference in the relative ease with which they are attacked by yeast, whilst the greater difference between glucose and talose is sufficient to inhibit the action of the ferment.

<sup>1</sup> Cf. Chap. xii.

Of the synthetically prepared sugars which contain more or less than six carbon atoms, it has been shown that the property of fermentation is restricted to those containing three, or a multiple of three, carbon atoms.

Similar selective actions have been studied in the hydrolysis of the simpler glucosides by enzymes. The name *glucoside* is a generic term for certain derivatives of the sugars which are widely distributed in the vegetable kingdom. Their chief characteristic is that they are decomposed by enzymes, as also by dilute acids or alkalis, with the formation of a sugar, which is very generally, but not always, glucose, and one or more other substances. The specific enzyme which effects this decomposition is always associated with the plants in which the glucosides occur. Many important natural plant products occur as glucosides; indigo is found in the indigofera as indican, alizarin in madder as ruberythric acid, oil of bitter almonds (benzaldehyde) in bitter almonds as amygdalin, and mustard oil in black mustard seeds as potassium myronate. Less complex compounds of an analogous chemical character have been prepared by the action of alcohols upon the aldo-hexoses;<sup>1</sup> like the natural glucosides, they can be hydrolysed into their constituents by the action of enzymes or of mineral acids.

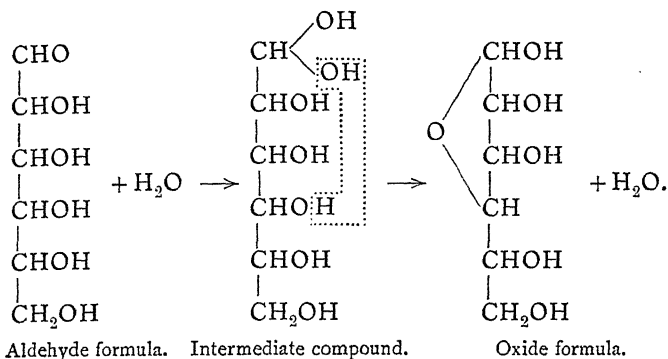
These synthetical compounds are ethers of glucose and its isomers; they are derived from an alternative formula for the aldo-hexoses to that given above. There is evidence that the glucose molecule, when in solution, has a different structure to that which it possesses when in the solid state, a view that has been specially brought home by the peculiar phenomena of *bi-rotation* or *muta-rotation*, which is shown by glucose and many other carbohydrates.<sup>2</sup> This phenomena consists in a change in optical activity which occurs when these compounds are dissolved in water; the optical activity of a freshly prepared solution of glucose, for instance, diminishes gradually on standing and finally becomes constant after about six hours,

<sup>1</sup> Emil Fischer, *Berichte*, 1893, xxvi. 2401; 1894, xxvii. 2985; 1895, xxviii. 1145.

<sup>2</sup> Cf. Lowry, *J. Chem. Soc.*, 1899, lxxv. 213; 1903, lxxxiii. 1314; and 1904, lxxxv. 1551. W. H. Perkin, *J. Chem. Soc.*, 1902, lxxxi. 177. Also Chap. xiv. pp. 387 and 388.

when the rotation is somewhat less than half that of the original solution. This change is attained practically instantaneously in presence of a small quantity of alkali.

The alternative formula for the aldo-hexoses is that of an oxide, which may be regarded as derived from the original aldehydic formula by the addition and subsequent separation of a molecule of water, the separation taking place between two hydroxyl groups in the  $\gamma$ -position to each other, the characteristic mode of anhydride or lactone formation that occurs with  $\gamma$ -hydroxy-acids.<sup>1</sup> These changes are represented by the following formulæ:—

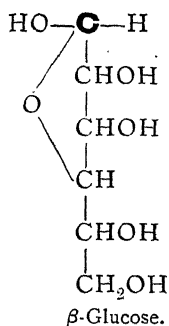
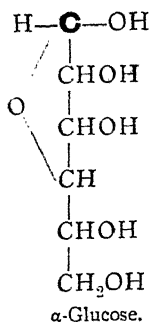


A new asymmetric carbon atom is introduced in this oxide formula, so that two stereochemical isomers are theoretically possible. These are called the  $\alpha$ - and  $\beta$ -forms, and the aqueous solution of glucose, when it has attained a constant optical rotation, is regarded as consisting of a mixture of the aldehydic and of these two oxide forms in a state of equilibrium.<sup>2</sup> In the following formulæ the added asymmetric carbon atom is indicated by thick type:—

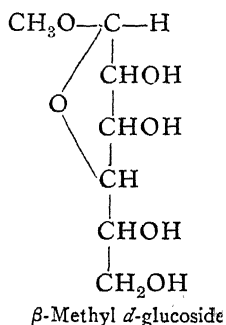
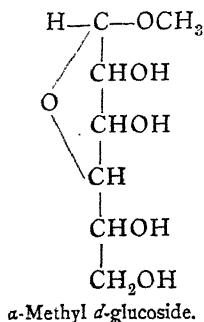
<sup>1</sup> Cf. Chap. viii. p. 157.

<sup>2</sup> Behrend and Roth (*Annalen*, 1904, cccxxxi. 359) have shown that glucose undergoes muta-rotation in pyridine solution and tetramethyl-glucose behaves similarly. (Purdie and Irvine, *J. Chem. Soc.*, 1904, lxxxv. 1049.) The presence of water may not, therefore, be essential for the formation of the equilibrium mixture.





The glucose ethers or glucosides, prepared by the action of alcohol upon glucose in presence of hydrochloric acid, have been obtained in the stereochemically isomeric  $\alpha$ - and  $\beta$ -forms; when hydrolysed by means of enzymes they yield solutions which contain initially the  $\alpha$ - or  $\beta$ -form of glucose respectively.<sup>1</sup> The formulæ of the two ethers or glucosides correspond, of course, to those of the two glucoses:—



Similar stereoisomers have been prepared by Fischer from  $L$ -glucose,  $d$ - and  $L$ -mannose and  $d$ -galactose. Although these  $\alpha$ - and  $\beta$ -compounds differ respectively only in regard to one asymmetric carbon atom, this difference suffices to inhibit their hydrolysis by enzymes

<sup>1</sup> E. F. Armstrong, *J. Chem. Soc.*, 1903, lxxxiii. 1305; and 1904, lxxxv. 1043. Behrend and Roth, *Annalen*, 1904, cccxxxi. 359.

into the sugar and alcohol. Maltase, the enzyme which effects the hydrolysis of maltose, for instance, converts  $\alpha$ -methyl-*d*-glucoside into glucose and methyl alcohol, but it has no action on the  $\beta$ -compound; emulsin, the enzyme contained in bitter almonds, on the other hand, only attacks the  $\beta$ -compound, and invertase does not attack either. Neither of the glucosides of *l*-glucose are attacked by either emulsin or maltase, but the  $\alpha$ - and  $\beta$ -*d*-galactosides behave like the *d*-glucosides. The alkyl derivatives of *d*- and *l*-mannose are not attacked by either maltase, emulsin, or invertase. Glucose and galactose accordingly appear to be the only hexoses, the glucosidic derivatives of which are attacked by the enzymes enumerated above; the small difference in configuration between mannose and these sugars is sufficient to completely inhibit enzymic hydrolysis. In the hydrolysis of the glucosides and galactosides the  $\alpha$ -compounds are attacked by maltase, but not by emulsin, whilst the reverse holds in the case of the  $\beta$ -compounds; since the hydrolysis is concerned only with the substituted hydroxyl group, and since these substances differ only in the configuration of this one group in the whole molecule, the intimate relation of the structure to the action of the ferment is strikingly apparent. It was suggested by Horace Brown and Glendinning,<sup>1</sup> from other considerations, that enzymic hydrolysis is preceded by a combination of the sugar with the specific enzyme that effects its hydrolysis; Fischer's investigations not only point to a confirmation of this view, but indicate further that such combination must take place along the entire chain of the hydrolysed molecule.

The enzymes, like proteins and protoplasm, are asymmetric products, and there is good reason to conclude that this selective action is to be attributed to the complementary configuration of the reacting molecules; as Emil Fischer has said, "Enzyme and glucoside must fit each other like key and lock in order that the one may exercise a chemical action on the other."

The subsequent investigations of E. F. Armstrong<sup>2</sup> have

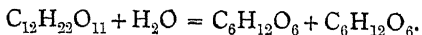
<sup>1</sup> *J. Chem. Soc.*, 1902, lxxxi. 388.

<sup>2</sup> *Roy. Soc. Proc.*, 1905, lxxvi., Series B, 592, 600; 1907, lxxix., Series B, 360.

served to confirm this idea of the initial combination of enzyme and glucoside, and have shown also that it extends to the products of decomposition by the enzymes. The action, for example, of emulsin on  $\beta$ -glucosides and  $\beta$ -galactosides is retarded both by glucose and by galactose, and that of maltase on the  $\alpha$ -compounds is similarly retarded by the same hexoses; in both cases the retarding effect of glucose is greater than that of galactose. These and other results show that the only hexoses which retard hydrolysis by a specific enzyme are those which result from the glucoside which undergoes hydrolysis under the influence of that enzyme.

The selective action of ferments is shown also in the oxidation of polyvalent alcohols, such as glycerol and mannitol to the corresponding ketoses, by the *sorbose acterium*.<sup>1</sup>

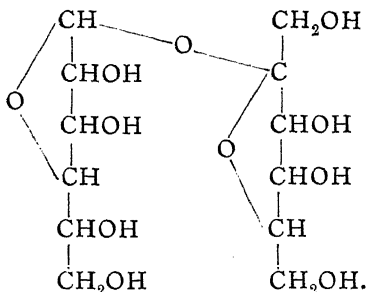
*The Di-hexoses: Saccharose, Lactose, and Maltose; their relation to the Hexoses.*—Cane sugar, milk sugar, and malt sugar, now known as saccharose, lactose, and maltose respectively, are not included in the classification of the sugars given above (p. 330). They form, together with other less known carbohydrates, a group called the *Di-hexoses*, which are characterised by being converted into hexoses by the action of dilute mineral acids or of ferments. They possess many of the properties of the hexoses, being weakly acidic, optically active compounds, readily soluble in water, sweet in taste, and generally more easily crystallised than the simpler hexoses. They have the general formula  $C_{12}H_{22}O_{11}$ , and their decomposition into hexoses takes place according to the equation:—



Cane sugar forms glucose and fructose, lactose forms glucose and galactose, and maltose two molecules of glucose. This decomposition is important as a means of arriving at the structure of the di-hexoses. It indicates that they are built up of two hexose molecules which are united with the elimination of a molecule of water, and as the hydrolysis is very readily effected, it is concluded that

<sup>1</sup> Cf. Bertrand, *Ann. Chim. Phys.*, 1904, iii. 181.

the hexose residues are held together by an oxygen atom, as the alkyl and hexose radicals in the simpler glucosides prepared by Fischer. They are thus anhydrides of the hexoses, and bear approximately the same relation to these as the ethers bear to the corresponding alcohols. Saccharose is the glucoside of fructose, lactose that of galactose, and maltose, glucose-glucoside. There are several ways in which this glucoside or anhydride formation can occur, and the study of the chemical properties of the di-hexoses has shown that it is different in cane sugar from what it is in lactose and maltose; the two latter retain one of the aldehyde groups of the constituent hexoses, whilst saccharose contains neither the aldehyde group of glucose nor the ketone group of fructose. The exact structural relations of these anhydrides to the simpler hexoses is not yet decided, but the following structural formula may be regarded as probable for saccharose:—



Saccharose or Cane sugar (Fructose glucoside.)

According to this formula saccharose should yield the  $\beta$ -modifications of glucose and fructose upon hydrolysis; it does not show muta-rotation, and has, therefore, probably the same structure both in solution and as a solid.<sup>1</sup>

The decomposition of cane sugar by dilute mineral acids is known as *Inversion*, a term which has its origin in the fact that the solution, which was originally dextro-rotatory, becomes lævo-rotatory upon hydrolysis; this is because the lævo-rotatory power of fructose is greater

<sup>1</sup> Cf. W. H. Perkin, *J. Chem. Soc.*, 1902, lxxx. 177.

than the dextro-rotatory power of glucose. This inversion is the basis of valuable analytical methods for the estimation of sugar. It is a uni-molecular reaction like the catalysis of the esters and the accelerating influence of acids can be similarly made use of for the measurement of their relative affinities.<sup>1</sup>

Although simple reactions are thus available for breaking up a di-hexose into two hexose molecules, the reverse change, or up-grade synthesis, has only been effected in a few instances. The first synthetically prepared di-hexose was obtained by Croft Hill<sup>2</sup> in experiments on the reversibility of enzyme action. He showed that the enzyme maltase, when allowed to act upon a concentrated solution of glucose, forms a mixture of di-hexoses, one of which is probably maltose; the same enzyme is also capable of converting maltose into glucose, and in both cases the same equilibrium mixture of the hexose and the di-hexose is established, which is dependent upon the concentration of the solutions. There is some doubt as to whether the di-hexose thus obtained is maltose or iso-maltose. This work is of special interest as being the first instance of the proof of the reversibility of enzyme action and the first application of enzymes as synthetic agents. The method has been extended by E. F. Armstrong,<sup>3</sup> who has obtained maltose by the action of emulsin upon glucose, and it has similarly been shown that another enzyme, kephir-lactase, partially converts galactose into a new di-hexose, iso-lactose.<sup>4</sup>

Other syntheses of di-hexoses have been effected by purely chemical reactions. Cane sugar, for instance, has been obtained by the mutual reaction between simple derivatives of glucose and fructose (Marchlewski, 1899), and a mixture of iso-maltose and maltose by the action of hydrochloric acid upon glucose.<sup>5</sup> Further, Emil Fischer and E. F. Armstrong<sup>6</sup> have prepared a glucoside of galactose and galactosides of glucose and of galactose; the galactoside of glucose is probably identical with meli-

<sup>1</sup> Cf. Chap. ix. p. 173.

<sup>2</sup> *J. Chem. Soc.*, 1893, lxxiii. 634; 1903, lxxxiii. 578.

<sup>3</sup> *Roy. Soc. Proc.*, 1905, lxxvi., Series B, 592.

<sup>4</sup> Emil Fischer and E. F. Armstrong, *Berichte*, 1902, xxxv. 3144.

<sup>5</sup> E. F. Armstrong, *loc. cit.*

<sup>6</sup> *Berichte*, 1901, xxxiv. 2885; 1902, xxxv. 3144.

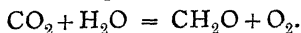
biose, a sugar obtained by the hydrolysis of a tri-hexose, raffinose.

Starch, dextrin, and gums resemble the di-hexoses in being hydrolysed by acids with the formation of one or more hexoses, and they are similarly decomposed by ferments, reactions upon which the fermentation and allied industries depend. They are more complex molecules than the di-hexoses, and are usually classed with cellulose as *Poly-hexoses*.

*The Building up of Carbohydrates in Plant Cells.*<sup>1</sup>—The 0.03 per cent. of carbonic acid in the air, kept in equilibrium by the mutual exchanges of plants and animals, is, together with water, the initial food for the building up of the carbohydrates.

Despite the achievements of the past twenty years in advancing the knowledge of their structure and synthesis, comparatively little is known of the processes of reduction in the living cells that precede the formation of sugar, starch, and cellulose. The very varied and intricate character of these changes and the fact that they are always associated with the presence of highly complex molecules, of which chlorophyll is the most characteristic, and with enzyme action, make it exceptionally difficult to obtain any insight into the constructive stages of plant assimilation. The earlier products of the change have, in all probability, only an ephemeral existence, so that special methods are required to remove them from the sphere of action as they are produced, in order to obtain satisfactory evidence of their formation.

The most generally accepted hypothesis of the nature of the change is that advanced by von Baeyer,<sup>2</sup> according to which the carbon dioxide is first reduced to formaldehyde, from which the carbohydrates result by polymerisation, the initial reduction taking place with liberation of oxygen, in accordance with the equation:—



Formaldehyde.

<sup>1</sup> Cf. Horace T. Brown, "Presidential Address to the Chemical Section of the British Association," *British Association Reports*, 1899, p. 682. Professor Meldola, "The Living Organism as a Chemical Agency," *J. Chem. Soc.*, 1906, lxxxix. 749.

<sup>2</sup> *Berichte*, 1879, iii. 66.

From the purely chemical side the possibility of this hypothesis is well established. Fenton<sup>1</sup> has shown that carbon dioxide can be reduced to formaldehyde at a low temperature in aqueous solution, and experiments by Bach<sup>2</sup> appear to prove that a similar reduction takes place when carbon dioxide is passed through a solution of a uranium salt, exposed to sunlight. The formation of acrose from formaldehyde by the action of a base was the first synthesis in the sugar group, and polymerisation and condensation, as characteristic properties of aldehydes, have also been instanced in the formation of a tetrose and of acrose from glycollic aldehyde. This latter aldehyde has been found as an intermediate product in the synthesis of sugar from formaldehyde, so that a satisfactory chain of laboratory evidence from carbon dioxide to fructose is thus completed. According to the investigations of Brown and Morris,<sup>3</sup> cane sugar is the primary carbohydrate that is formed in plants; fructose, dextrose, and maltose are also present in the green leaf, whilst the more complex carbohydrates, starch and cellulose, are the characteristic final products of assimilation. Despite numerous hypothetical suggestions, the laboratory syntheses of these products from fructose have hardly been approached, beyond the few isolated methods described in connection with the preparation of the di-hexoses from hexoses (p. 352); satisfactory chemical evidence of the nature of these later stages is accordingly at present wanting. It is also probable that intermediate reduction products, between carbon dioxide and formaldehyde, are formed in the earlier stages of assimilation, which may also lead to the formation of carbohydrates as well as to that of the characteristic acids found in plants, such as oxalic acid, by their action upon each other or upon carbonic acid itself.

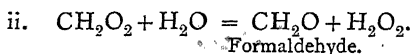
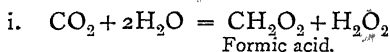
The conditions under which laboratory methods have been able to give support to von Baeyer's hypothesis are, of course, entirely different to those that obtain in the natural synthesis of carbohydrates in living plants, and until recently there has been no satisfactory physiological

<sup>1</sup> *J. Chem. Soc.*, 1907, xci. 687.

<sup>2</sup> *Comptes rend.*, 1893, cxvi. 1145; cf. Usher and Priestley, *Roy. Soc. Proc.*, 1906, lxxvii, Series B, 369.

<sup>3</sup> *J. Chem. Soc.*, 1893, lxiii. 604.

evidence in its favour. A number of experiments have been carried out on feeding plants with formaldehyde and its simpler derivatives, which have shown that certain plants can form starch when treated in this manner. Such evidence, however, is only indirect, because the formaldehyde may itself be first polymerised to a sugar, independently of the vital action of the plant, and it is known that plants can form starch from sugar in absence of light. More direct and complete evidence of the nature of the changes during assimilation has now been established by the investigations of Usher and Priestley,<sup>1</sup> who have proved the presence of formaldehyde as an initial change in the reduction of carbon dioxide by plants, on exposure to sunlight. Its production is accompanied by the formation of hydrogen peroxide, which is decomposed by a special enzyme with the liberation of oxygen, whilst the formaldehyde is taken up by the living protoplasm and polymerised with the formation of carbohydrates. The reduction of the carbon dioxide takes place, in sunlight, with leaves in which both the enzymes and the protoplasm have been killed by immersion in boiling water, so that the change appears to be independent of the vitality of the leaf. These results have been confirmed by Usher and Priestley in a most interesting manner, by allowing carbon dioxide to act upon thin films of chlorophyll, under conditions approaching those under which it is present in the green leaf. On exposing such films to sunlight, formaldehyde and hydrogen peroxide are formed, and by introducing a suitable catalysing enzyme, oxygen is liberated from the latter. Further, they have shown that in presence of certain kinds of living protoplasm, free from chlorophyll, starch and oxygen are the final products of the assimilation, as in the case of growing plants. Formic acid appears to be an intermediate product in the initial reduction of the carbon dioxide to formaldehyde, so that this stage in the assimilation is to be represented by the equations:—

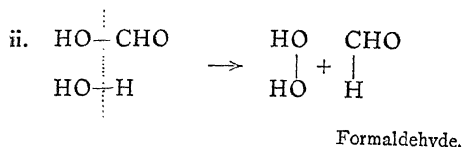
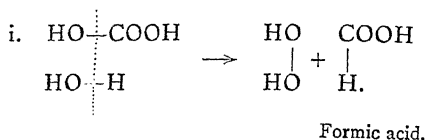



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<sup>1</sup> *Roy. Soc. Proc., Series B*, 1906, lxxvii. 369; lxxviii. 318.



The formation of the hydrogen peroxide and accompanying reduction of the carbon dioxide, which thus occurs under the influence of the chlorophyll acting as a catalyst, is probably due to a combination of the hydroxyl groups, first of the water and carbonic acid and then of the water and formic acid, as indicated in the following equations:—



The chemical evidence of the nature of the subsequent stages in assimilation is very deficient, as stated, and on the physiological side this deficiency is, at present, still more marked.

A further problem of great interest connected with plant assimilation lies in the fact that all the carbohydrates that occur in nature are not only optically active, but that they are found in but one of the enantiomorphously related configurations. All the natural sugars and starches are derived from *d*-glucose, and amongst many other groups of compounds the same relation holds; the albumins, the alkaloids, the terpenes, and organic acids such as tartaric and malic, are represented in nature by only one of the stereochemical isomers.

The asymmetric compounds obtained by means of symmetrical reactions from symmetrical compounds, on the contrary, are always formed as an optically inactive mixture made up of equal proportions of the two enantiomorphs, as in the case of racemic acid; these can be separated by an enantiomorphous agency according to the methods already described, but in no instance is a single asymmetric molecule the direct result of a laboratory synthesis from symmetrical compounds.

This difference was clearly recognised by Pasteur, whose view, however, that the molecular asymmetry of natural organic products was the most characteristic distinction between the chemistry of living matter and the chemistry of dead matter<sup>1</sup> was generally regarded as untenable after the complete synthesis of racemic acid and its separation into the two stereochemical isomers. Pasteur did not accept this interpretation, and pointed out that an important difference still remained, which he expressed in the following words:—"To transform one inactive compound into another inactive compound, which has the power of resolving itself simultaneously into a right-handed compound and its opposite, is in no way comparable with the possibility of transforming an inactive compound into a single active compound. This is what no one has ever done; it is, on the other hand, what living nature is continually doing before our eyes."

The action of enzymes, the formation of salts with an optically active base or acid, the mechanical separation of the enantiomorphous salts that separate out as in the crystallisation of sodium ammonium racemate, which constitute the available methods for the isolation of single optically active molecules from the products of synthetical reactions, are all to be referred back to life. The enzymes are products of vital processes; optically active acids and bases owe their initial origin to Nature, and the mechanical separation of two crystal forms is the specific act of a living organism.<sup>2</sup>

To account for the fact that only single enantiomorphs are found as the result of animal and vegetable metabolism, one or both of two processes are possible. It may be that compensated mixtures are first formed, which are subsequently resolved into their components, the one isomeride being separated and the other used for purposes that are at present unknown. Or, there may be selective production only, owing to the asymmetric environment in which the vital processes occur, for there

<sup>1</sup> Cf. Chap. xii. p. 298.

<sup>2</sup> Cf. Japp, "Presidential Address to the Chemical Section of the British Association," *British Association Reports*, 1898, p. 813. Also *Nature*, 1898, lviii. 452, and subsequent correspondence; W. J. Pope, *Nature*, 1903, lxviii. 280; and Byk, *Z. physik. Chem.*, 1904, xlix. 641.

is ample evidence that "asymmetry begets asymmetry." The syntheses carried out by McKenzie,<sup>1</sup> with the object of ascertaining whether an asymmetric carbon atom already present in a molecule has any directing influence upon the introduction of new groups, have proved that a preferential formation of one of the two possible isomers does occur. Such syntheses are, as yet, far less complete than those concerned with the formation of carbohydrates under natural conditions, but they indicate the probability that the condensation of the formaldehyde may be preceded by a combination with some optically active constituent of the chlorophyll granules, the asymmetric influence of which leads to the production of single enantiomorphs.

<sup>1</sup> Cf. Chap. xii. p. 301.

## CHAPTER XIV.

### ISOMERIC CHANGE AND DYNAMIC ISOMERISM.

*Isomeric Change.*—Unknown compounds, the possible existence of which is indicated by the law of the linking of atoms—Isomeric change involving the movement of a hydrogen atom—Compounds which form two series of isomeric derivatives—Laar's tautomeric compounds.

*Reversible Isomeric Change or Dynamic Isomerism.*—The isomeric relations of acyl derivatives of methane, of diacetyldiethylsuccinate and of nitro-compounds—Theoretical considerations regarding dynamic isomerism—The application of chemical methods to the study of dynamic isomerism.

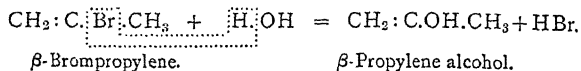
*The relation of the Physical Properties of Organic Compounds to their Structure and the application of this relation to the study of Dynamic Isomerism.*—The refraction constant—The magnetic rotation of the plane of polarisation—The optical rotatory power—The selective absorption of light—The electrical conductivity of organic compounds—The solubility.

*The bearing of Dynamic Isomerism on the Structure of Benzene and some of its derivatives.*

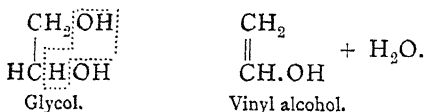
THE general method adopted in organic chemistry for deciding the structure of compounds consists in the study of the reactions that serve for their preparation and of the changes they undergo in their various decompositions. Many instances of this method have been given in the previous chapters; the syntheses of isobutane, acetic acid, lactic acid, and racemic acid, for example, leave no doubt as to their structural formulæ, and are, moreover, in complete agreement with all that is known of their chemical character and products of decomposition. Whenever such accord exists between the syntheses, properties, and decompositions of a compound there is no difficulty in thus deciding its structure.

But many reactions are known which, if interpreted on the normal lines of analogous changes, would lead to

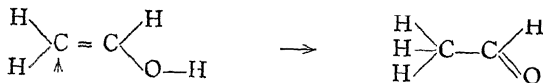
wrong conclusions in regard to the structure of the resulting compounds. Thus, when  $\beta$ -bromopropylene is heated with water it would be expected to form an unsaturated alcohol, according to the following equation:—



And, similarly, the removal of a molecule of water from glycol should yield the simplest of the unsaturated alcohols, vinyl alcohol:—



But these and other reactions that might lead to the formation of such unsaturated alcohols always result in the formation of their respective isomers, acetone and acetaldehyde. The conclusion is therefore drawn that the atomic groupings of  $\beta$ -propylene alcohol and of vinyl alcohol are unstable, and that at the moment of their isolation they are immediately changed into the stable molecules acetone and acetaldehyde. This change, as shown in the following formulæ, involves the movement of a hydrogen atom and a consequent alteration in the disposal of the valencies of carbon and oxygen, the double bond between two carbon atoms becoming a single bond, and the oxygen atom, previously linked to hydrogen as hydroxyl, changing to the ketonic form of combination:—



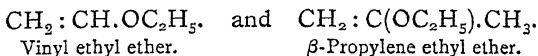
Vinyl alcohol.

Acetaldehyde.

 $\beta$ -Propylene alcohol.

Acetone.

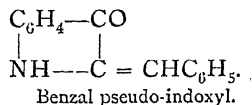
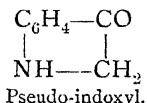
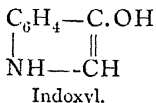
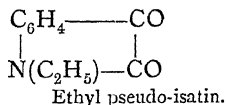
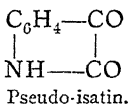
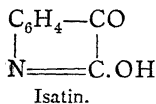
Although these isomers of acetaldehyde and acetone, which are theoretically possible according to the law of the linking of atoms, are too unstable for separate existence, simple derivatives of them are known—for instance, their ethyl ethers:—



These ethers readily lose the ethyl group on treatment with dilute mineral acid, and then form acetaldehyde and acetone respectively. The isomeric ethyl homologues of acetaldehyde and acetone (butyl aldehyde and methyl propyl ketone) are well-defined stable compounds.

The replacement of the hydrogen atom, which is very light, by the heavier ethyl group, in the above unsaturated alcohols, thus allows of the separate existence of isomers, the mother substances of which are not known;<sup>1</sup> or, in other words, whilst only one mother substance can be isolated, two isomeric series of derivatives can be obtained.

This peculiar isomeric relationship has been observed amongst many groups of organic compounds. In his investigations on indigo von Baeyer<sup>2</sup> pointed out that certain compounds of the indigo group, which were only known in one of the two possible isomeric forms, were capable of yielding two series of derivatives. Thus, isatin and indoxyl have theoretically possible isomers, to which von Baeyer gave the names pseudo-isatin and pseudo-indoxyl, derivatives of which such as ethyl pseudo-isatin and benzal pseudo-indoxyl are known:—



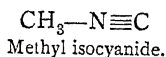
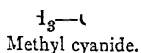
These hypothetical pseudo-forms von Baeyer regarded as unstable molecules which in the free state revert

<sup>1</sup> Cf. Chap. viii. p. 127.

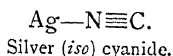
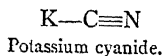
<sup>2</sup> *Berichte*, 1883, xvi. 2188.

ously into the original form, and he attributed the change to the mobility of the hydrogen atom, since substitution of the latter by alkyl or aryl groups induces stability. This relation corresponds exactly to that of the unsaturated alcohols referred to above, and the change from the pseudo- to the normal-form similarly involves the wandering of one of the hydrogen atoms, and is accompanied by a readjustment of the atomic linkings.

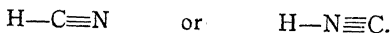
*Laar's Tautomeric Compounds.*—In a paper entitled "On the possibility of several Structural Formulæ for one and the same Chemical Compound,"<sup>1</sup> Laar (1885) grouped together a number of compounds, which show this isomeric relationship, and with the view of expressing its special character he suggested the term *Tautomerism* for the phenomenon (from ταυτό, the same; μέρος, a part). Tautomeric substances, according to Laar, were compounds which, although only known in one form, give rise to two types of derivatives, and amongst other substances he instanced hydrocyanic acid and several simple cyanogen compounds as examples of this relationship. Thus hydrocyanic acid itself is the mother substance of both the cyanides and the isocyanides. These compounds are prepared by the action of alkyl iodides upon potassium and silver cyanide respectively, and there is ample evidence to prove that they have the following structural formulæ<sup>1</sup>:—



From their methods of preparation it might be concluded that potassium and silver cyanide have the respective constitutional formulæ:—



Since these salts can be obtained directly from hydrocyanic acid, either of the following formulæ might represent the structure of the one hydrocyanic acid that is known:—



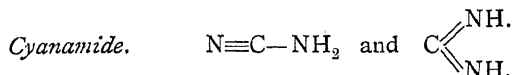
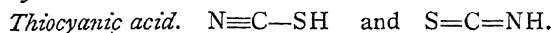
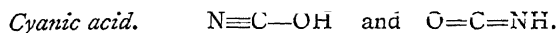
<sup>1</sup> *Berichte*, 1885, xviii. 648 and  
<sup>2</sup> *Cf.* Chap. x. pp. 193.

## ISOMERIC CHANGE AND DYNAMIC ISOMERISM.

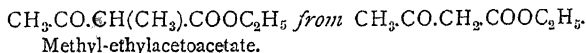
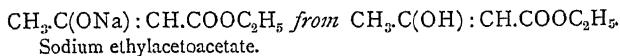
In the one formula the hydrogen atom is attached to carbon, in the other to nitrogen. As in the examples given above, a change from one to the other form involves the movement of a hydrogen atom and the readjustment of the atomic linkings. A similar interpretation is necessary if carbon be regarded as divalent in the isocyanides. The attempt to decide between these alternative formulæ has given rise to important theoretical considerations which will be discussed presently, after some further examples of this isomeric relationship have been described.

Amongst other cyanogen compounds which show a similar behaviour to hydrocyanic acid, cyanic acid, thiocyanic acid and cyanamide may be instanced. Here again only one mother substance is known, but two isomeric series of derivatives have been prepared.

The following are the alternative structural formulæ for these compounds:—



Some of the most interesting instances of this kind of isomerism have been observed amongst a rather complex group of compounds, of which ethylacetoacetate is the best known. It has already been pointed out in the discussion of the structure and reactions of this compound that there is good reason to regard the salts it forms with sodium and other metals as derived from a structural formula different from that from which its alkyl derivatives are obtained,<sup>1</sup> *e.g.* :—

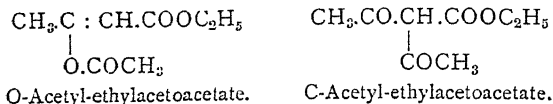


The unsaturated hydroxylic formula is called the “*enol*” form, the ketonic formula the “*keto*” form. The alkyl

<sup>1</sup> Cf. Chap. ix. p. 182.



compounds are all derived from the keto-form of the ester, but acetyl and other acyl (the term *acyl* is used generically for an acid radical) derivatives of both forms are known,<sup>1</sup> viz.:—



The acetyl group is linked to oxygen in the one case (called the O-derivative), to carbon in the other (called the C-derivative); when sodium ethylacetoacetate is treated with acetyl chloride, the C-compound is formed almost exclusively; but when ethylacetoacetate is mixed with the base pyridine, and the acid chloride added to the mixture, the O-derivative is obtained.<sup>2</sup> Hence it is concluded that ethylacetoacetate, which is only known in the form of a liquid which distils with slight decomposition at 181°, shows a two-fold chemical character in its reactions, according to the nature of the substances with which it combines, or the conditions under which a derivative is prepared.

*Reversible Isomeric Change or Dynamic Isomerism.*<sup>3</sup>—So far the special isomeric relations exemplified by the above compounds are quite analogous; one, and only one, mother substance is known, whilst derivatives of the two possible structural isomers have been isolated. An important development of the subject has more recently (since 1896) been attained by the investigations of Claisen, Knorr, and Wislicenus amongst a number of compounds of similar chemical character to that of ethylacetoacetate, the most interesting outcome of which has been the successful isolation of the structurally isomeric forms of the mother substances. Similar results have also been obtained amongst nitro-compounds by Hantzsch and by Lowry.

This shows that the so-called tautomerism of such

<sup>1</sup> Note.—An ethyl-O-ethylacetoacetate has been prepared, but not directly from the ester. Cf. Claisen, *Berichte*, 1893, xxvi. 2731.

<sup>2</sup> Claisen and Haase, *Berichte*, 1900, xxxiii. 1242.

<sup>3</sup> A valuable summary of this subject is given by T. M. Lowry: "Dynamic Isomerism," *British Association Reports*, 1904, p. 193.

compounds is only a peculiarly subtle form of isomerism, and that if the requisite precautions are taken the possible isomers indicated by the law of the linking of atoms can be isolated. Its special importance lies, however, in the fact that it has given the key to a proper understanding of the isomeric relations of compounds which exhibit a two-fold chemical character. Considerable confusion has been introduced into the study of the subject by attempts to differentiate the nature of the relation where two or more mother substances are known from that observed with hydrocyanic acid and ethylacetoacetate, the terms "*relative tautomerism*" and "*desmotropism*" having been suggested for the former, and "*absolute tautomerism*," or simply "*tautomerism*," for the latter. But the phenomena connected with these relations are all quite similar in character; they differ only in degree, not in kind, and nothing is gained by such attempts at subdivision. Amongst the many suggested terms for this special isomerism,<sup>1</sup> that of *Dynamic Isomerism*, which is due to Lowry, is the most appropriate; it expresses the peculiar isomeric relations and mutually reversible changes that exist amongst most of the compounds concerned very significantly, as will be subsequently shown.

The experimental data on which the present view of this phenomenon is based can be advantageously exemplified by Claisen's<sup>2</sup> work on certain acyl derivatives of methane, by Knorr's<sup>3</sup> investigations on diacetyldiethyl succinate, and by Lowry's<sup>4</sup> and Hantzsch's<sup>5</sup> studies on nitro-compounds.

*The Isomeric relations of Acyl derivatives of Methane, of Diacetyldiethyl succinate, and of Nitro-compounds.*—Claisen examined the isomeric relations of the following three methane derivatives, in each of which three hydrogen atoms of the methane molecule are replaced by acid radicals:—

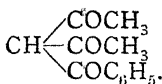
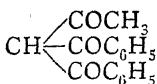
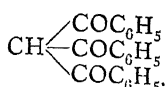
<sup>1</sup> "Tautomerism," "desmotropism," "metamerism," "pseudoisomerism," "merotropism," etc.

<sup>2</sup> *Annalen*, 1896, ccxci. 25.

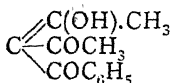
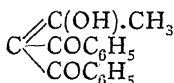
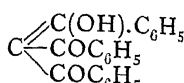
<sup>3</sup> *Annalen*, 1896, ccxciii. 70; and 1899, cccvi. 332.

<sup>4</sup> *J. Chem. Soc.*, 1899, lxxv. 235.

<sup>5</sup> *Berichte*, 1896, xxix. 699 and 2251; 1898, xxxi. 2854; 1899, xxxii. 575, 1723, and 3066; 1900, xxxiii. 278.

Diacetyl-benzoyl  
methane.Acetyl-dibenzoyl  
methane.Tribenzoyl  
methane.

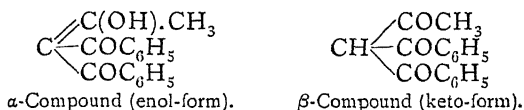
All these compounds form sodium salts, similarly to ethyl-acetoacetate, and it is accordingly assumed that these metallic compounds are derived from the following isomeric or enolic formulæ:—

Diacetyl-benzoyl  
methane.Acetyl-dibenzoyl  
methane.Tribenzoyl  
methane.

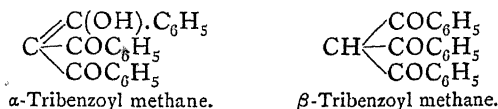
Only one diacetyl-benzoyl methane is known; it is a crystalline substance which, from its chemical behaviour and physical properties, is regarded as having the enolic structure. The second compound, acetyl-dibenzoyl methane, as prepared by the addition of acetic acid to its sodium salt, is a crystalline solid, melting at  $99^\circ$ - $101^\circ$ ; it dissolves readily in alkalis and alkaline carbonates, and in solution gives a red coloration with ferric chloride. When, however, its solution in dilute alcohol is allowed to cool, the crystals that separate have a higher melting point,  $107^\circ$ - $110^\circ$ ; they further differ from the original substance by being insoluble in dilute sodium carbonate solution, and in not giving any coloration with ferric chloride. This same change occurs gradually on prolonged standing, and is effected at once when the first compound is heated to  $70^\circ$ . On the other hand, when the second compound is heated to  $110^\circ$ , it is partially converted into the product of lower melting point. The two compounds have been satisfactorily proved to have the same composition and molecular weight; they are isomers, characterised by being readily converted one into the other. Their chemical behaviour is similar except for the two reactions mentioned above; they are, therefore, regarded as fulfilling the conditions of linking required by the isomeric, enolic, and ketonic formulæ. Since the compound melting at  $99^\circ$ - $101^\circ$ , which is distinguished as the  $\alpha$ -compound, shows acid

properties by its ready solubility in alkalis, the enolic formula is assigned to it. This view is confirmed by the reaction with ferric chloride, since many hydroxy-compounds, especially those of the aromatic group, such as phenol, give a coloration with this reagent. The term "enol" is derived from this relation. Solubility in dilute sodium carbonate solution (1 per cent.) and a coloration with ferric chloride are regarded as the characteristics of enolic compounds, but the interpretation of the action of these reagents requires caution, because they may themselves be the cause of isomeric change.  $\beta$ -acetyl-dibenzoyl methane, the isomer of higher melting point which is regarded as the ketonic compound, is, for instance, gradually dissolved by alkaline carbonates and by alkalis, but on acidifying the resulting solution the  $\alpha$ - or enolic-form is separated; it is thus possible to "enolise" the ketonic isomer. Similarly, a coloration with ferric chloride is produced when the  $\beta$ -compound is left in contact with this reagent for some time.

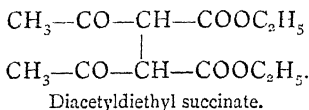
The isomerism of these two compounds is, accordingly, represented by the following structural formulæ:—



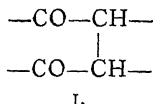
The third compound investigated by Claisen, tribenzoyl methane, is also known in two forms, which differ similarly to the above in melting point and in their behaviour towards alkalis and ferric chloride. The enolic form ( $\alpha$ ) is relatively very unstable; on being kept for two days it changes almost completely into the ketonic compound ( $\beta$ ). The isolation of these two isomers, the formulæ of which are given below, is especially interesting, because there is no possibility of their being stereo-isomers; this possibility exists with the two previous compounds, although it is quite inconsistent with their relative chemical behaviour:—



Knorr's investigations on diacetyldiethyl succinate involve more complex isomeric relations.<sup>1</sup> This compound has the formula:—



prepared by the action of iodine upon the sodium ethylacetoacetate; it is the diethyl-ester of the derivative of succinic acid. No less than thirteen isomeric forms of this compound are theoretically possible, three of which are different in respect to the linking of the contained atoms, the remainder being stereo-isomers. These isomeric relations centre in the group:—



By the movement of one or of both of the hydrogen atoms of this group the following two isomeric formulæ arise:—



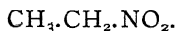
I. is a double keto-form, III. a double enol-form, whilst II. represents a mixed, keto-enol compound. I. contains two asymmetric carbon atoms like tartaric acid, and consequently four stereo-isomers can be derived from it (inclusive of the racemic combination); II. and III. allow of the possibility of three and six stereo-isomers respectively.

Of the thirteen isomers, seven are optically inactive, and no fewer than five of these have been isolated by Knorr. There is naturally very considerable difficulty in assigning the correct formulæ to isomers which are so closely related, and which, in addition, are readily converted into

<sup>1</sup> *Berichte*, 1897, xxx. 2387; *Annalen*, 1899, cccvi. 332.

one another; but from their reactions with ferric chloride and their relative behaviour towards alkalis and alkaline carbonates, two of these compounds, known as the  $\alpha_1$  and  $\alpha_2$  forms, are regarded as having the double enolic structure (III.); one,  $\alpha_3$ , appears to be a keto-enol form (II.); and the remaining two ( $\beta$  and  $\gamma$ ) diketo-forms (I.). With the exception of the  $\alpha_1$ -compound, which is a liquid, and possibly a mixture, they are all crystalline substances of definite melting point, and show different solubilities in certain solvents, especially in petroleum spirit. The most important and interesting fact that has been established by the study of these compounds is that when any one of them is dissolved in the same solvent and left in solution for a sufficient length of time, a mixture of identical composition results. When benzene or chloroform is employed as the solvent, the proportion of the ketonic to the enolic forms is 1 to 1; when ether or petroleum spirit is used, it is 7 to 3. These proportions are hardly influenced either by changes of temperature or by varying the concentration of the solutions. When heated individually, they all first form a similar mixture, in which the ketonic and enolic forms are present in the ratio of 2 : 3; on prolonged heating the other isomers are gradually and completely changed into the  $\beta$ -compound. Other interchanges of a similar character can be effected by various reagents and solvents.

The isomeric relations observed amongst certain nitro-compounds are quite analogous. For instance, nitroethane and phenylnitromethane form salts with alkalis which were formerly represented by the formulæ:—



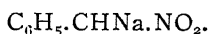
Nitroethane.



Sodium nitroethane.



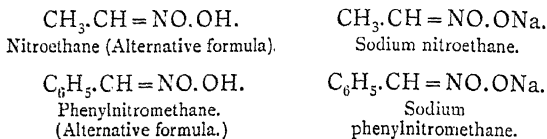
Phenylnitromethane.



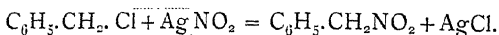
Sodium phenylnitromethane.

As in the case of ethylacetoacetate, it was assumed that the close proximity of an electronegative radical (in this case the  $\text{NO}_2$  group) imparted acidic properties to a hydrogen atom in the  $\text{CH}_2$  group. In conformity with the view since accepted for the structure of the metallic salts of ethylacetoacetate and similar compounds, these sodium

derivatives of nitro-compounds are now also regarded as derived from an alternative or pseudo-formula containing an hydroxyl group:—

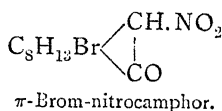
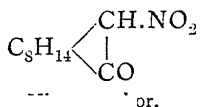


In addition to these sodium compounds, several other derivatives of these nitro-compounds are known, the structure of which can only be explained by the hydroxylic formula, thus indicating the two-fold chemical character of the mother substance; in the case of phenylnitromethane and some of its substitution products both isomers are known. Phenylnitromethane is prepared by the action of silver nitrite on benzyl chloride, according to the equation:—

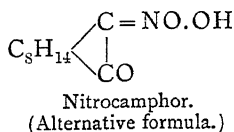


It forms a liquid, which boils at  $226^\circ$ , and dissolves slowly in sodium hydroxide to form the sodium salt. When this solution is acidified by carbonic acid, the original product is regenerated; but if hydrochloric or other strong mineral acid be used for the decomposition of the sodium salt, a crystalline isomer is obtained melting at  $84^\circ$ . These crystals revert to the liquid nitro-compound on standing or when dissolved; they give a coloration with ferric chloride, whereas the liquid form does not react with this reagent. The latter is, therefore, regarded as containing the normal nitro-group, whilst the hydroxylic or enolic formula is assigned to the solid isomer. The change from the enolic to the ketonic form is said to be complete and not reversible, thus differing from the instances given above; but it is more probable that a small proportion of the less stable or labile isomer is present in the liquid product. All isomeric changes are most likely accompanied by some amount of reversal, although it may be too little to be detected by the methods at present available. That such mixtures do arise amongst nitro-compounds has been fully proved by Lowry's study of

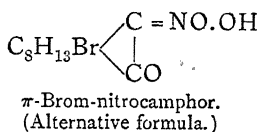
two camphor compounds, nitrocamphor and  $\pi$ -brom-nitrocamphor:—



The alternative formulæ for these compounds are:—



and



The investigations on brom-nitrocamphor are specially complete. Three isomers of this compound were originally described, melting at  $108^\circ$ ,  $126^\circ$ , and  $142^\circ$  respectively, of which the first and last form well-defined crystals. The subsequent study of these compounds has shown that there are really only two isomers, the third, that of melting point  $126^\circ$ , being a mixture, which is obtained when either of the other forms is fused, or is separated from solution by rapid evaporation. The isomer of higher melting point ( $142^\circ$ ) is much the less soluble of the two; both have the same molecular weight, and when dissolved the two modifications ultimately yield identical solutions. Ferric chloride, which in most cases is a useful reagent for distinguishing isomers of this type, gives a coloration with both compounds, and no difference could be detected in the depth of the colour produced or in the velocity with which it is formed. This behaviour is unusual, and is to be attributed to the accelerating, catalytic effect of ferric chloride on the isomeric change. Nor has it been possible to differentiate these isomers by other chemical reagents, but this has been successfully effected by considerations bearing on the muta-rotation the two forms show when dissolved, as will be pointed out in connection with the application of physical methods to the determination of the structure of dynamic isomerides (p. 389).

*Theoretical Considerations regarding Dynamic Isomerism.*  
—The above examples of dynamic isomerism represent



only a few of the types of compounds in which the phenomenon has been established, but all exhibit one and the same characteristic, the change from one isomer to another involving the movement or wandering of a hydrogen atom and the readjustment of the atomic linkings in the molecule.

When ketonic compounds change to the enolic form this characteristic is represented by the atomic rearrangement:—



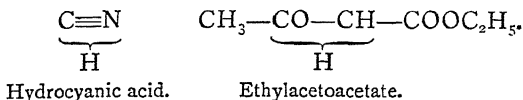
which is reversed when the enolic isomer is ketonised. Similarly, the change of a nitro-compound to the hydroxylic or pseudo-form follows the course:—



These isomeric changes are in every way analogous to those of hydrocyanic acid and of the unknown isomers of acetaldehyde and acetone. They are concerned clearly with the movement of the atoms within a molecule, and their study is a dynamic problem, as distinct from the static considerations that obtain with the law of the linking of atoms and with stereochemical isomerism. Hence the term “dynamic isomerism” is especially appropriate. Not that dynamic considerations do not enter into all other chemical reactions, such as substitution, reduction, oxidation and the like, but because the separate existence of isodynamic forms is specially governed by the relative atomic movements within the molecule.

The original hypothesis advanced by Laar to account for the fact that one mother substance could form two series of derivatives was that the “tautomeric” compound really consists of two forms which continually pass into one another by the movement or vibration of a hydrogen

atom. Hydrocyanic acid and ethylacetoacetate, for instance, were looked upon as substances which, instead of possessing a definite structure, oscillated backwards and forwards between the alternative structural formulæ, as represented by the symbols :—



This view embodied the idea that such compounds were homogeneous molecules, whilst it avoided any conclusion as to their specific structure. The isolation of dynamic isomerides effected by Knorr, Claisen, Hantzsch, Lowry and others has, apart from other considerations, rendered this hypothesis untenable; isodynamic forms have been shown to exist as distinct substances in the crystalline state possessing individual physical and chemical properties. Each isomer has a definite structure, but when fused or dissolved a reversible isomeric change sets in and a condition of equilibrium between the isodynamic forms becomes established. This isomeric relation has been proved to exist in all those cases of dynamic isomerism in which two or more isomers have been obtained in the crystalline state. In the case of liquids, such as ethylacetoacetate, one or more isomers may be present, and in the latter instance the several forms will exist side by side in a state of equilibrium. The proportions of the isomers present under these conditions of equilibrium may show the greatest variations. In extreme cases, say of a compound of which only two isomeric forms are possible, the proportion of one of these may be so small as to be practically negligible. This condition may be regarded as a limiting case of dynamic isomerism, and it is represented by the unknown isomers of acetaldehyde and acetone.

This view of dynamic isomerism rests upon sound experimental data, of which the examples detailed above are typical. That a condition of equilibrium can exist between isomeric compounds was proved long ago by Butlerow (1877), as the outcome of a most valuable research on *Isodibutylene*,<sup>1</sup> and it is now well established

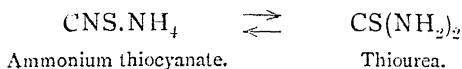
<sup>1</sup> *Annalen*, 1877, clxxxix. 44.

that these conditions obtain when isodynamic compounds are melted or dissolved; they are only somewhat masked by such physical properties as solubility or melting point. In the case of diacetyldiethyl succinate, for example, all the isomers are gradually and completely converted into the  $\beta$ -, diketo-form, but this in no way disproves the existence of a condition of equilibrium. The change is due solely to the fact that this form is the least soluble, and has the highest melting point, and therefore separates from the mixture most readily, either when the latter is dissolved or heated. As the least soluble isomer separates out, a readjustment of the equilibrium occurs, with the formation of a further quantity of this isomer, which continues to separate out in the same way, and thus the whole of one or more of the other forms passes gradually and completely into the  $\beta$ -compound. Nor does this indicate that the  $\beta$ -isomer is the most stable of the five; on the contrary, the mixture of identical composition obtained from any of the isomers, when dissolved, always contains as much, sometimes more than thrice as much of the enolic forms, according to the solvent employed. The principle is exactly analogous to that which determines the precipitation of inorganic salts which, as is well known, depends upon their solubility and not upon their stability. The real dynamic isomerism of these compounds, of which two or more mother substances are known, exists, therefore, only when they are dissolved or melted; when isolated in the crystalline state they are simply structurally isomeric compounds. The possibility of isolating dynamic isomerides must consequently be determined chiefly by the temperature at which they become isodynamic and the velocity of the change. Several instances are known of isomeric compounds which are quite stable at the ordinary temperature but which become isodynamic upon heating. For example, the preparation of thiourea from ammonium thiocyanate, a change which is analogous to Wöhler's synthesis of urea,<sup>1</sup> is really a reversible isomeric change<sup>2</sup>:—

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<sup>1</sup> Cf. Chap. x. p. 218.

<sup>2</sup> Reynolds and Werner, *J. Chem. Soc.*, 1903, lxxxiii. 1; and A. Findlay, *J. Chem. Soc.*, 1904, lxxv. 403.



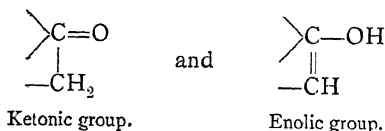
When either of these compounds is fused it is partially converted into the isomeride, and in each case a product consisting of about 75 per cent. of the thiocyanate and 25 per cent. of thiourea is formed. This represents a condition of equilibrium of the same character as that observed with the isodynamic compounds described above. The change from the one isomer to the other is not, however, dependent only upon the movement of a hydrogen atom; it involves a more complex molecular rearrangement. Also, each isomer is sufficiently stable at the ordinary temperature to be easily separated by chemical methods.

Between such conditions of isodynamic change and those which occur with moderate velocity at ordinary temperatures many intermediate stages are possible, and at the opposite extreme the dynamic isomerism of substances, such as hydrocyanic acid and ethylacetoacetate, which are only known in the form of physically homogeneous liquids, is reached. The separation of the isomers in such equilibrium mixtures has not yet been possible, and in fact it is only by special methods that their presence and proportions can be determined. If, however, these relations could be studied at temperatures considerably below the normal it is highly probable that many of the compounds which are ordinarily regarded as labile could be readily separated as distinct and stable isomers.

*The Application of Chemical Methods to the Study of Dynamic Isomerism.*—Two chemical reactions have been described above for the differentiation of isodynamic compounds—namely, solubility in dilute sodium carbonate solution and the formation of a coloration with ferric chloride. When the extreme conditions can be realised these reactions are satisfactory. Where both isomers are known and the one is not affected by either of these reagents it can safely be regarded as the ketonic form; but in many cases their accelerating influence on the isodynamic change destroys the specific value of the

reactions. The coloration with ferric chloride, as a test for the presence of the enolic form, is the more reliable of these two reactions, as it is produced by the conversion of only a small quantity of the substance into the ferric salt, and not only has it been of value for the recognition of enolic isomers, but also as a means of following the gradual enolisation of the ketonic forms<sup>1</sup>; still, in some instances the accelerating effect of the ferric chloride on the isomeric change is so rapid, as in the case of brom-nitrocamphor, that the reagent fails to differentiate the two isomers, whilst the reaction is also greatly influenced by the nature of the solvent used. With homogeneous liquids like ethylacetoacetate, which show isodynamic relations at the ordinary temperature, these reagents can, at most, indicate the presence of one of the isomers, but not the absence of the other; ethylacetoacetate gives an immediate reaction with ferric chloride, showing that the liquid may contain the enolic modification, but this in no way proves that the compound is wholly made up of this form. There is, in fact, much other evidence to show that the ketonic form greatly preponderates in this compound.

Apart from these comparatively simple reactions, it would at first sight appear quite easy to distinguish the presence of an hydroxyl and of a carbonyl group in enolic and ketonic isomers. Each of these groups is:—



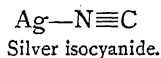
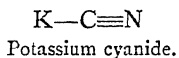
gives specific reactions with a variety of reagents, several of which have already been considered. Ketones react with hydroxylamine to form oximes, with phenyl hydrazine to form hydrazones; alcohols form acetyl compounds, sodium salts, and other acid derivatives, whilst the two groups are, in addition, differentiated by the action of phosphorus pentachloride.<sup>2</sup> Moreover, there are many reactions which serve for the recognition of an ethylene bond such as is present in the enolic compounds, but

<sup>1</sup> Cf. Wislicenus, *Berichte*, 1899, xxxii. 2837; 1900, xxxiii. 125.

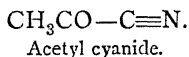
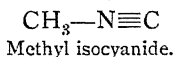
<sup>2</sup> Chap. viii. p. 143.

absent in the keto-forms. A little consideration, however, will show that reactions of this character must of necessity be inconclusive. In the first place, they practically always necessitate, either solution, or the employment of a temperature above the melting point of the compound investigated, so that whether the substance is isodynamic at the ordinary temperature or not, the experimental conditions involve the reaction taking place in presence of an equilibrium mixture of the two isomers. Secondly, although only one of the isomers in this mixture may be able to enter into chemical combination with the reagent employed, it can only do so by disturbing the condition of equilibrium in the mixture. This condition will be continuously re-established as the combination takes place; further portions of the reactive isomer will then enter into combination, and thus the whole of the original product may be gradually converted into a derivative of one isomer only, just as Knorr's  $\beta$ -diacetyldiethyl succinate is formed when the other isomers are heated or dissolved.

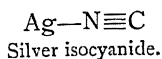
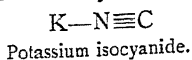
Further, whilst a reagent might be expected to react only with one isomer, the other modification may also take part in the change, apart from any structural alteration in the initial molecule, owing to the possible formation of intermediate additive compounds. An instance of this was given in the preparation of the alkyl derivatives of ethylacetoacetate from its sodium salt,<sup>1</sup> and it is well exemplified in the isomeric relations of the inorganic and organic cyanides. Potassium and silver cyanide yield isomeric compounds when treated with an alkyl iodide, whence, as stated above (p. 362), the conclusion might be drawn that the silver salt has the isocyanide structure:—



The alkyl compounds obtained from silver cyanide are, undoubtedly, isocyanides, but acid chlorides, such as acetyl and benzoyl chloride, react with silver cyanide to form normal cyanides:—



Similarly, potassium cyanide in many of its properties shows an isocyanide structure, although its reaction with alkyl iodides points to its being a normal cyanide. It thus appears that each of these two salts yields derivatives of two types. The above reactions, therefore, do not suffice to decide between the alternative formulæ for the salts, and still less are they of value as evidence of the structure of hydrocyanic acid itself. Other chemical changes are more definite in their character, and the balance of facts is favourable to the view that both potassium and silver cyanide are isocyanides<sup>1</sup>:—



This is in accordance with the structure which has been deduced for hydrocyanic acid itself from considerations of its acidic strength and of its electrical conductivity.<sup>2</sup>

The formation of alkyl isocyanides can proceed directly from compounds of this structure; to account for the formation of normal cyanides it is suggested that intermediate additive compounds are formed.

Attempts have been made to differentiate dynamic isomerides by means of reagents which combine with both the enolic and ketonic modifications simultaneously, but which lead to the formation of different compounds in the two cases, the one ketonic and the other enolic. This method was applied to decide the proportions of the two forms contained in ethylacetoacetate.<sup>3</sup> From the previous considerations it is obviously fallacious, but the experiments involved are of interest because they showed that the presence of only a trace of an added base governed the nature of the resulting compound. When ethylacetoacetate is treated with benzal-aniline, for instance, a substance that can react with both enolic and ketonic compounds, the resulting product is a solid melting at 103°, but when a trace of the base, piperidine, is present an isomer melting at 80° is obtained;<sup>4</sup> which of these

<sup>1</sup> Wade, *J. Chem. Soc.*, 1902, lxxx. 1596.

<sup>2</sup> Chap. x. p. 193. Cf. also Nef, *Annalen*, 1892, cclxx. 329; 1895, cclxxxvii. 325.

<sup>3</sup> Schiff, *Berichte*, 1898, xxxi. 601.

<sup>4</sup> F. E. Francis, *Berichte*, 1903, xxxvi. 937; and *J. Chem. Soc.*, 1904, lxxxv. 998.

compounds is the ketonic and which the enolic form has not been decided. This base has a similar influence, it will be remembered, in the preparation of the C-acetyl derivatives of the ester. Such catalytic reagents condition the chemical behaviour of other dynamic isomerides, and it is probable that they function through the formation of intermediate additive compounds;<sup>1</sup> the results prove nothing, however, in regard to the structure of the original substance.

Catalytic reagents not only condition the chemical behaviour of dynamic isomerides, but appear to be essential for the establishment of equilibrium. It has been shown<sup>2</sup> that the most easily convertible compounds do not change spontaneously, but that a catalytic agent is in all cases necessary for a reversible isomeric change to occur. The amount of the catalyst required to establish equilibrium may be extremely, almost inconceivably, small; in the case of nitrocamphor the addition of 0.0001 per cent. of piperidine is sufficient to effect this in two or three hours, and in other instances the solvent action of a solution of one of the isomers on the glass of the containing vessel will suffice. The action of ferric chloride on brom-nitrocamphor (p. 371) is a further instance of this catalytic effect.

The necessity for the presence of a catalytic agent is accordingly regarded as a characteristic of dynamic isomerism; the phenomenon is, therefore, an intermolecular process, and not an intramolecular change, as required by Laar's hypothesis of the oscillation of a hydrogen atom within the molecule.

The value of chemical agents for deciding the structure of dynamic isomerides is, from the foregoing considerations, clearly very restricted. When the conditions of reaction are such that the isomeric change proceeds slowly, they provide a useful means for separating the constituents of an equilibrium mixture; but since the majority of chemical agents act catalytically as accelerators of isomeric change, this application is also of limited value.

<sup>1</sup> Cf. Lowry, *J. Chem. Soc.*, 1899, lxxv. 241.

<sup>2</sup> Lowry, *J. Chem. Soc.*, 1899, lxxv. 219; and *British Association Reports*, 1904, p. 193.



*The Relation of the Physical Properties of Organic Compounds to their Structure, and the Application of this Relation to the Study of Dynamic Isomerism.*—Owing to the limitations of the chemical methods as a means of determining the structural relations of isodynamic compounds, other methods have been sought which are free from the disturbing influences that of necessity arise when chemical changes are involved. Such independent criteria obtain in the study of the physical properties of organic compounds, for they can be investigated without the intervention of any extraneous reagent. They have been shown to stand in close relation to the structure of compounds, and since the development of the subject of dynamic isomerism these properties themselves, and the changes they undergo under the influence of heat or of solvents, have proved of great value for the recognition of the presence and proportions of isodynamic compounds.

Kopp (1842) was the first to draw attention to the importance of the relation of the physical properties of compounds to their structure,<sup>1</sup> and his views were eagerly studied and extended as a welcome aid in solving the complexities of organic chemistry. This study and extension brought many irregularities to light, and led to a more accurate determination of physical constants than had been previously carried out. The result of these later investigations has been to show that the relation between physical properties and chemical structure is far more restricted in character than had been supposed, and that marked limitations attend its application. These limitations are now fully recognised, and with their recognition certain physical properties have again taken rank as a means of elucidating structural problems.

The physical properties of compounds are distinguished as *additive*, *constitutive*, and *colligative*.<sup>2</sup> Mass is an example of a purely additive property; substances containing the same number of like atoms have all the same molecular weight, however these constituent atoms are arranged. Such properties can give no insight into the structure of compounds. Constitutive physical properties

<sup>1</sup> Cf. Thorpe, "Kopp Memorial Lecture," *J. Chem. Soc.*, 1893, lxiii. 775.

<sup>2</sup> Cf. Chap. v. p. 76.

depend not only upon the number and kind of the atoms present in a molecule, but show variations according to the manner in which these atoms are linked together. The melting point and boiling point are good instances of constitutive physical properties;<sup>1</sup> also the molecular refraction and molecular volume, which have been referred to in respect to their bearing on the structure of benzene.<sup>2</sup> All these properties are more or less additive in character as well, but they depart from purely additive properties, such as mass, by showing constitutive variations according to the manner in which the atoms of a compound are united. These constitutive influences are the valuable factors in the study of the relation of physical properties to the structure of compounds. Colligative properties, such as the molecular volume of gases, are the opposite of additive properties; they are independent of the number and nature of the atoms in a molecule; like purely additive properties, they have no bearing on structure.

The most important constitutive physical properties in relation to dynamic isomerism are the refraction constant, the magnetic rotation of the plane of polarisation, the optical rotatory power, the selective absorption of light, the electrical conductivity, and the solubility; to these may be added the heat of formation of compounds, which has already been considered in its bearing on the structure of ethylene, acetylene, and benzene.<sup>3</sup> Other physical properties, such as the molecular volume, crystalline form, the viscosity and the surface tension of liquids, have also been shown to bear certain, more or less definite, relations to the structure of compounds, but they are more limited in this respect than the above.

*The Refraction Constant.*—The refractive power is an expression of the velocity of light in a transparent substance, and is ascertained by measuring the deviation of a ray of light in passing from one medium into another. To carry out the measurement, the liquid to be examined is placed in a hollow, glass prism and the deviation of a monochromatic beam of light determined. The sine of the angle of incidence of the light always bears a

<sup>1</sup> Cf. Chap. vi. pp. 82 and 86.

<sup>2</sup> Cf. Chap. v. p. 76.

<sup>3</sup> Chap. iv. p. 56; and Chap. v. p. 76.

constant ratio to the sine of the angle of refraction, and this ratio, which represents the relative velocities of light in the two media, is known as the index of refraction. The velocity of light in air is taken as the unit = 1, and such an expression as  $n = 1.3606$ , for ethyl alcohol, signifies that the relative velocity of light in alcohol and in air is represented by the ratio  $\frac{1}{1.3606}$ . The refractive index of a

liquid varies both with the wave-length of the light and with the temperature. In order to avoid the first of these influences, it is always measured for light of definite wave-length, usually the red hydrogen line (H $\alpha$ ) or the yellow sodium line (D $_1$ ). The influence of temperature on the refractive index was investigated by Gladstone and Dale (1858), who showed that the expression  $\frac{n-1}{d}$ , in which  $n$ ,

represents the index of refraction and  $d$ , the density of the liquid at the temperature of the experiment, is practically independent of temperature. They, therefore, regarded this factor, which is known as the *Refraction constant*, as the real measure of the refractive power. Later investigations have shown that a somewhat more complex formula is a more correct expression of the refraction constant.<sup>1</sup> The product of the refraction constant and the molecular weight is called the "molecular refractive constant," or "molecular refraction." This factor was at first looked upon as a purely additive property, the refraction constant for a compound being regarded as equal to the sum of the constants of its constituent elements. The refraction constants for the elements can only be arrived at indirectly, and the method adopted is typical of that generally employed in the study of the relation of physical properties to the composition of compounds.

Amongst the aliphatic alcohols, the fatty acids and their ethereal salts, there is an average increase of 7.6 units in the molecular refractive constant between the successive members of each homologous series. This value represents, therefore, the molecular refractive constant of the

<sup>1</sup>  $\frac{n^2 - 1}{(n^2 + 2)d}$ . Suggested from theoretical considerations, independently, by Lorenz and Lorentz (1880).

group  $\text{CH}_2$ . The constant obtained by experiment for acetic acid,  $\text{C}_2\text{H}_4\text{O}_2$ , is 21.1; by subtracting  $2 \times 7.6$  ( $=\text{CH}_2 \times 2$ ) from this value, the constant for  $\text{O}_2$  is obtained, and from this the atomic refraction of oxygen. This is, therefore, equal to  $5.9 \div 2 = 2.95$ ; the average value, similarly calculated, from a number of other compounds is 3. The atomic refraction of hydrogen and of carbon can be derived on analogous lines from the molecular refraction constants of the alcohols. The value for ethyl alcohol,  $\text{C}_2\text{H}_6\text{O}$ , is 20.70; subtracting  $2\text{CH}_2 = 7.6 \times 2$  and  $\text{O} = 3$ , the constant for  $\text{H}_2 = 2.5$  is obtained, and the atomic refraction for hydrogen, 1.25 (1.3 is the average value). Finally, with  $\text{CH}_2 = 7.6$  and  $\text{H}_2 = 2.6$ , the difference represents the atomic refraction for carbon as equal to 5.

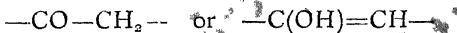
The additive character of this constant can be illustrated in the case of ethyl acetate,  $\text{CH}_3\text{COOC}_2\text{H}_5$ . Calculated from the elements, it should be:—

$$4\text{C} + 8\text{H} + 2\text{O} = (4 \times 5) + (8 \times 1.3) + (2 \times 3) = 36.4,$$

the value actually found being 36.17.

Brühl, however, pointed out that the above atomic constants are but an incomplete representation of this physical property, and that the refraction constant, instead of being purely additive, shows marked constitutive variations amongst different classes of compounds. The atomic refraction of oxygen, for instance, varies with its condition of combination; when combined with hydrogen in the hydroxyl group, it is smaller (2.75) than when in direct combination with carbon in the carbonyl group,  $\text{C}=\text{O}$ , (3.4). Similarly, different values arise for singly, doubly, and trebly linked carbon atoms, and for ter- and quinquivalent nitrogen. These are the valuable constitutive factors of refraction which are of service in deciding the structure of compounds.

The isomeric forms of the ketonic esters of the type of ethylacetoacetate contain one or other of the groups:—



The calculated molecular refraction for the ketonic formula will differ from that for the enolic owing to the presence of

a double linking between the two carbon atoms, and of hydroxylic in place of carbonyl oxygen in the latter, the actual figures being 31.78 and 32.72 respectively. Brühl<sup>1</sup> found the molecular refraction, as determined by experiment at the ordinary temperature, to be 31.99, and concluded, therefore, that the ester is essentially ketonic; he also confirmed the ketonic formula for the alkyl derivatives of ethylacetoacetate by determinations of their molecular refraction.<sup>2</sup>

The calculated values of these physical constants for more complex ketones, such as diacetyldiethyl succinate, are obtained by extrapolating the values derived from simpler compounds, but in such cases the method is open to the criticism that the other groups present may influence the physical property examined. This objection applies to all constitutive physical properties, but any changes these properties undergo under the action of heat or solution are altogether free from such influences, and the evidence such changes afford of reversible isomeric change in equilibrium mixtures of isomers has consequently been recognised as an important additional means of applying the physical properties of compounds to the investigation of dynamic isomerism. Thus, in the case of the diacetyldiethyl succinates the refraction constant of the enolic ( $\alpha$ ) forms is greater than that of the ketonic ( $\beta$ ) isomer. The latter, when dissolved in ether, alcohol, or acetone, shows a small increase in the value of the constant, which indicates its partial conversion into the enolic form; and when either the  $\beta$ - or the  $\alpha_1$ -isomer is dissolved in chloroform and allowed to stand for 120 hours, the refraction constant is found to be the same in the two cases, showing that an equilibrium mixture of identical composition has been formed by a reversible isomeric change between the two compounds.<sup>3</sup>

*The Magnetic Rotation of the Plane of Polarisation.*—The phenomenon of the magnetic rotation of the plane of polarisation, discovered by Faraday in 1846, has been the subject of a very complete series of investigations by

<sup>1</sup> *Berichte*, 1892, xxv. 366.

<sup>2</sup> *Berichte*, 1894, xxvii. 2378.

<sup>3</sup> Knorr, *Annalen*, 1899, cccvi. 359.

Sir W. H. Perkin in respect to its bearing on the structure of compounds.<sup>1</sup>

Transparent substances, when brought into a magnetic field or into the interior of a coil of wire conducting an electric current, acquire the power of rotating the plane of polarised light, and retain this power whilst the electromagnetic action lasts. The conditions influencing the angle of rotation have been carefully examined, and they are fully taken into account in computing the values for the *Molecular magnetic rotation* of compounds, in which the rotation due to the molecule equivalent of water (18 grams) is taken as the unit. The experimental results show that the magnetic rotation is a much more strongly marked constitutive property than the refraction constant, and in the aliphatic group especially this constitutive influence shows distinct and applicable regularities. The additive nature of the property is shown in the general formula for aliphatic compounds:—

$$\text{Molecular magnetic rotation} = .1.023,$$

in which  $n$  is the number of  $\text{CH}_2$  groups present in the molecule, and  $C$  a constant, which varies for each homologous series; the latter expresses the constitutive influence. By means of this formula the position of a compound in its group, or the actual group in which it should be classed, can be checked by a determination of its magnetic rotatory power.

Perkin has, in addition, given special attention to the magnetic optical activity of isomeric compounds. All unsaturated compounds have a greater magnetic rotatory power than the corresponding saturated substances, and by considering the changes in this property that accompany the substitution of a hydrogen atom by the characteristic isomeric groups of the ketonic esters,  $-\text{CO}-\text{CH}_2-$ , and,  $-\text{C}(\text{OH})=\text{CH}-$ , a reliable basis has been established for calculating the rotatory power of either the ketonic or the enolic form of dynamic isomers. The value for the latter is about 20 per cent. greater than that for the former, the calculated figures in the case of ethylacetoacetate

<sup>1</sup> *J. Chem. Soc.*, 1884, v. 421; 1892, lxi. 800; 1894, lxxv. 815; 1896, lxxix. 1025.

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being 6.510 and 7.849 for the ketonic and enolic forms respectively. The molecular magnetic rotation for this compound, as determined by experiment, is 6.502 at 15° and 6.448 at 91°, showing that at both these temperatures it is essentially a saturated ketone; the small decrease in the rotatory power at the higher temperature is observed with all compounds to about this extent. The alkyl derivatives of ethylacetoacetate are also ketonic compounds, according to the measurements of their magnetic rotation. These results are fully in accord with the conclusion derived from the determination of the refractive

constants.

Whilst the normal change in magnetic rotation on heating, observations on compounds containing ketonic groups have established very valuable evidence the presence of mutually convertible isomers, and have, in addition, shown the influence of substituents on the relative stability of the ketonic and enolic forms. The following experimental data obtained with acetylacetone (diacetylmethane) and its monomethyl and dimethyl derivatives illustrate these relations:—

	Temperature.	Molecular Rotation.	Difference for 100°.
Acetylacetone ...	16°.7 90°	7.175 6.599	0.755
Methyl-acetylacetone...	17°.4 96°.4	7.290 6.670	0.785
Dimethyl-acetylacetone	19°.3 92°.3	7.042 6.995	0.064

These compounds each contain two ketonic groups like diacetyldiethyl succinate and might have, similarly, a double ketonic, a keto-enolic, or a double-enolic structure, represented in the case of acetylacetone by the following formulæ:—

- I.  $\text{CH}_3 \cdot \text{CO} \cdot \text{CH}_2 \cdot \text{CO} \cdot \text{CH}_3$ . Di-ketonic formula.
- II.  $\text{CH}_3 \cdot \text{C}(\text{OH}) : \text{CH} \cdot \text{CO} \cdot \text{CH}_3$  Keto-enolic formula.
- III.  $\text{CH}_3 \cdot \text{C}(\text{OH}) : \text{C} : \text{C}(\text{OH}) \cdot \text{CH}_3$ . Di-enolic formula.

The molecular rotation for each of these forms can be calculated on the lines indicated above. When compared with the figures obtained experimentally they show that at the ordinary temperature acetylacetone consists of an equilibrium mixture containing 80 per cent. of the keto-enolic form (II.), and 20 per cent. of the di-enolic form (III.); monomethyl-acetylacetone consists of 46.4 per cent. of the di-ketonic form (I.), and 53.6 per cent. of the keto-enolic form, whilst the dimethyl compound is wholly di-ketonic. The decrease in the magnetic rotation on heating indicates the formation of the ketonic from the hydroxylic groups in the case of acetylacetone and the monomethyl compound; the change in the case of dimethyl-acetylacetone is not greater than that generally observed with an increase of temperature, and, as in the case of ethylacetoacetate, it shows that there is no appreciable change in the composition of the equilibrium mixture at the higher temperature. The introduction of alkyl groups, therefore, decreases the relative stability of the enolic forms of these compounds, and this influence has been observed with several other similarly constituted substances. That the thermic changes in the molecular rotation are really concerned with an alteration in structure is confirmed by the observation that the magnetic rotatory power of these compounds, after being heated and then allowed to cool, remains lower than it was originally; it is only after a considerable interval, in some cases days, in others weeks, that it returns to its initial value, or, in other words, that the original conditions of equilibrium are restored.

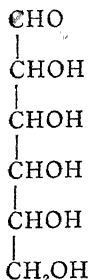
The magnetic rotatory power has also been applied to the study of the phenomenon of the muta-rotation of the carbohydrates,<sup>1</sup> and the results obtained show that the characteristic change that is observed in the optical rotation of these compounds, when dissolved, is due to an alteration in structure. In the case of glucose, for instance, the experimental determination of the molecular magnetic rotation gave the value 6.723; the calculated value for the ordinary aldehyde formula (I.) is 6.913, that for the oxide formula (II.), from which the ethers of glucose are derived,<sup>2</sup> about 6.7. Hence, it is concluded

<sup>1</sup> W. H. Perkin, *J. Chem. Soc.*, 1902, lxxxi. 177.

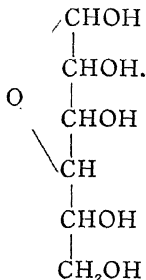
<sup>2</sup> Cf. Chap. xiii. p. 347.



that solutions of glucose, after all change has taken place, consist of an equilibrium mixture containing essentially the oxide forms with probably a small proportion of the aldehydic isomer.



I. Aldehyde formula.



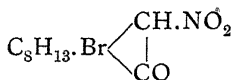
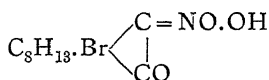
II. Oxide formula.

The results show quite definitely that muta-rotation is not due to the hydration of the glucose molecule as was formerly considered probable. It has similarly been shown, from determinations of the magnetic rotation, that the muta-rotation of fructose, galactose, lactose, and maltose is, in each case, consistent with the view that an isomeric molecular change takes place in solution.

*The Optical Rotatory Power.*—The rotation of the plane of polarisation of a beam of light is a constitutive property dependent upon the presence of an asymmetric atom. Experiments by Guye and others have shown that this property is to some extent additive also, but the regularities are not sufficiently established to warrant very definite conclusions on this point.<sup>1</sup> On the other hand, the changes in rotatory power that occur when certain substances are dissolved, the phenomenon of muta-rotation, is an important means for the recognition of the presence of dynamic isomerides; its value is added to by the fact that such isomerides usually show considerable differences in their rotatory power and by the rapidity and accuracy with which the necessary measurements can be made. The muta-rotation of the carbohydrates has been referred

<sup>1</sup> *Comptes rend.*, 1890, cx. 714; 1895, cxx. 157, 452, 632, 1274 and intervening papers.

to in respect to their structure<sup>1</sup> and their magnetic rotatory power. The view that the muta-rotation of these compounds is due to a reversible isomeric change was first put forward by Lowry,<sup>2</sup> who based his conclusion on the muta-rotation of brom-nitrocamphor, which he satisfactorily proved to be due to the formation of an isodynamic mixture. It will be remembered that there are two forms of  $\pi$ -brom-nitrocamphor known (*cf.* p. 371), which melt at  $142^\circ$  and  $108^\circ$  respectively; they differ also in their solubilities and in their crystalline form. The compound of higher melting point has an initial rotatory power in a 3.33 per cent. benzene solution of  $+188^\circ$ , which changes to  $-38^\circ$  in a little more than two days; the isomer melting at  $108^\circ$  has an initial rotatory power in like solution of  $-50^\circ$ , which after a similar interval becomes constant at the same value,  $-38^\circ$ . These figures represent what is known as the *specific rotatory power* of optically active substances. It is usually represented by the symbol  $[\alpha]$ , or by  $[\alpha]_D$  when sodium light is used in the measurement; this value is obtained by dividing the actual rotation observed in the polarimeter by the length of the layer of liquid through which the light passes and by the density of the liquid at the temperature of the observation; the length is generally expressed in decimetres. From a comparison with the rotatory powers of other members of this group of compounds it is concluded that the dextro-rotatory isomer is the pseudo- or hydroxylic form, the lævo-rotatory form, the normal nitro-compound:—

Normal  $\pi$ -Brom-nitrocamphor.M.P.  $108^\circ$   $[\alpha]_D - 50^\circ$ Pseudo-  $\pi$ -brom-nitrocamphor.M.P.  $142^\circ$   $[\alpha]_D + 188^\circ$ .

Knowing the rotatory power of each isomer, the composition of the equilibrium mixture obtained in benzene solution can be calculated from the observed rotation; this corresponds to seventeen parts of the normal and one part of the pseudo-form. The simpler camphor derivative, nitro-camphor, is only known in one form; it is a lævo-

<sup>1</sup> *Cf.* Chap. xiii. p. 346.<sup>2</sup> *J. Chem. Soc.*, 1899, lxxv. 211.

rotatory, crystalline solid, and is regarded as the normal compound. It shows muta-rotation in solution, similarly to its bromine derivative, but the proportion of the two isomers in the equilibrium mixture varies with the nature of the solvent, as does the time taken before the equilibrium is established. These changes are consistent with the occurrence of an isomeric change in solution.

The muta-rotation of the sugars is very satisfactorily explained from this standpoint of isodynamic change. The isolation of the oxide-forms of glucose in the solid state has been effected,<sup>1</sup> and these, when dissolved, form the same equilibrium mixture as that obtained from ordinary glucose.<sup>2</sup> Judged by the rotatory power, the equilibrium mixture contains 36.7 parts of the aldehydic form and 63.3 of the oxide isomers,<sup>3</sup> a larger proportion of the former than is indicated by the magnetic rotation; the rate of change is approximately the same with each modification.

The optical rotatory power has more recently been made use of in a different manner for the study of isodynamic changes. It has been known for some time that the rotatory power of a compound may be influenced to a considerable extent by the presence of certain optically inactive substances, and, on this basis, Patterson and Macmillan<sup>4</sup> have worked out a method for following the changes of dynamic isomers, such as phenylnitromethane and thiourea, by dissolving them in an optically active solvent, such as ethyl tartrate, and determining the gradual alteration in activity.

*The Selective Absorption of Light.*—Investigations on the colour of organic compounds have shown that this property is to a large extent constitutive, additive relations being observable only amongst closely related compounds; some reference is made to this in connection with the coal tar dyes.<sup>5</sup> Differences in colour have also been observed as a characteristic of the normal and hydroxylic or pseudo-

<sup>1</sup> Tanret, *Comptes rend.*, 1895, cxx. 1060; E. F. Armstrong, *J. Chem. Soc.*, 1903, lxxxiii. 1305; and Behrend and Roth, *Annalen*, 1904, cccxxxi. 359.

<sup>2</sup> Cf. Chap. xiii. p. 347.

<sup>3</sup> Roux, *Ann. Chim. Phys.*, 1903, xxx. [7] 422.

<sup>4</sup> *J. Chem. Soc.*, 1907, xci. 504; 1908, xciii. 1041.

<sup>5</sup> Cf. Chap. xv. pp. 421 and 430.

forms of many isodynamic nitro-compounds, and have been useful in following the progress of isomeric change.

Apart from the selective absorption of light rendered evident by colour, many compounds possess selective absorptive power for ultra-violet light. This property, which was discovered by Stokes (1852), has been studied in detail by Hartley and Dobbie<sup>1</sup> amongst cyclic compounds.

Many of these are characterised, not only by a powerful absorption of the most refrangible rays, but also by showing absorption bands when dissolved in water, alcohol or ether, even in very dilute solution: Stereo-isomers, which differ only in their optical rotation and crystalline form, show no differences in selective absorption, but isomers in which there is a difference in the linking of the constituent atoms and geometrical isomers such as fumaric and maleïc acids, are characterised by different absorption spectra.<sup>2</sup> The property is essentially constitutive in character, and is, therefore, applicable to the differentiation of isodynamic compounds in solution. It has been studied amongst several groups of dynamic isomerides, including an analogue of diacetyldiethyl succinate, the corresponding dibenzoyl compound. Of the thirteen theoretically possible dibenzoyldiethyl succinates three have been prepared by Knorr,<sup>3</sup> to two of which he assigned a ketonic formula, to the third the enolic structure. This conclusion is fully confirmed by their selective absorption of ultra-violet light. The two ketonic forms, which are regarded as stereo-isomers, show the same absorption band in alcoholic solution; with the enolic form this band is absent, and is replaced by a band in a different position in the ultra-violet spectrum. Further, it was found possible to follow the gradual transition from the enolic to the ketonic form, in alcoholic solution, by photographing the spectra at successive intervals of time; the results are entirely in accord with the progress of the change observed by means of the ferric chloride reaction.

<sup>1</sup> *J. Chem. Soc.*, 1899, lxxv. 640; 1900, lxxvii. 318, 498, 509, 839, 846; 1901, lxxix. 848; 1902, lxxxi. 929; 1905, lxxxvii. 1822. Also Hartley, *British Association Reports*, 1903, p. 583.

<sup>2</sup> Magini, *J. Chem. Soc. Abstracts*, 1904, lxxxvi. 107.

<sup>3</sup> *Annalen*, 1896, ccxciii. 70.

The relation of the structure of isatin (p. 361) to that of its alkyl derivatives has been similarly determined by an appeal to the absorption spectra of these compounds. Methyl isatin and methyl pseudo-isatin show distinctly different absorptions; the absorption spectrum of isatin resembles that of the latter. Hence, it is concluded that the one known form of this substance consists essentially of the pseudo-isomer.<sup>1</sup>

More recently Baly and Desch<sup>2</sup> have recorded a series of very interesting observations on the ultra-violet absorption spectra of ethylacetoacetate, acetylacetone, and other analogous, isodynamic compounds. Their experiments show that neither the pure ketonic nor the pure enolic forms of substances of this type give any absorption band, but that their sodium, aluminium, and other metallic salts show characteristic band spectra in dilute solution. Since these absorption bands appear only with the salts and not with the parent compounds, nor even when the ketonic and enolic forms of the latter are mixed together, it is concluded that they are produced by an intramolecular movement connected with the change from one modification into the other. It is not considered probable that this movement consists of the vibration of the metallic atom in the molecule, because the absorption is nearly independent of the mass of the metal present; it is regarded as due to the change in linking of the carbon and oxygen atoms as the bonds pass backwards and forwards between the ketonic and enolic forms. Apart from this hypothesis of the origin of the absorption bands, which requires further support, this phenomenon, when more fully investigated, is likely to throw considerable light on the mutual changes of dynamic isomerides.

*The Electrical Conductivity of Organic Compounds.*—With the exception of acids, bases, and salts, most organic compounds are not electrolytes either in solution or when melted;<sup>3</sup> the former, like the similar inorganic substances, are more or less dissociated in solution, and thus give rise to free ions, which, according to the Arrhenius

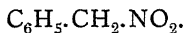
<sup>1</sup> Cf. Hartley, *British Association Reports*, 1903, p. 583.

<sup>2</sup> *J. Chem. Soc.*, 1904, lxxxv. 1029; 1905, lxxxvii. 766; 1906, lxxxix. 489.

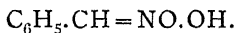
<sup>3</sup> Cf. Chap. xi. 269.

theory of electrolytic dissociation, are essential for the carrying of the electric current.<sup>1</sup> Electrical conductivity is, therefore, a constitutive property, and it is one that has been successfully applied to the study of the structure of compounds.<sup>2</sup> Thus, the conductivity of diazobenzene chloride (phenyl diazonium chloride) and analogous salts is quantitatively similar to that of the salts of the inorganic bases, sodium and potassium hydroxide, an analogy on which the diazonium formula of these compounds is based;<sup>3</sup> similarly, the salts of the amino-derivatives of triphenylmethane are regarded as derived from a true ammonium base,<sup>4</sup> since determinations of their electrical conductivity show that they are not hydrolysed in solution, a characteristic of the salts of all strong bases.

The difference in structure of most dynamic isomerides is due to the presence of an acidic radical in the one form which is absent in its isomer, and in such cases the validity of this relation can be tested experimentally by a determination of the electrical conductivity, since the acidic compound and its salts should behave as electrolytes in solution, whilst the non-acidic form should be a non-conductor of electricity. Thus, in the case of the two phenylnitromethanes:—



Normal compound.



Pseudo-compound.

the latter, from which the sodium salt is regarded as derived, is acidic in structure, and should accordingly act as an electrolyte. Hantzsch<sup>5</sup> has studied this relation with phenylnitromethane and a number of analogous nitro-compounds, and has shown that their salts behave as neutral salts in solution, being therefore derived from moderately strong acids, and that when these salts are acted upon by a mineral acid to form the free nitro-compound this is initially separated in the acidic or pseudo-form, but passes with greater or less speed into

<sup>1</sup> Cf. Chap. xi. p. 270.

<sup>2</sup> Cf. *Electrochemistry*, R. A. Lehfeldt, 1904, Chap. ii.: "The Relation of Chemical Constitution to Conductivity," by T. S. Moore.

<sup>3</sup> Cf. Chap. x. p. 212.

<sup>4</sup> Cf. Chap. xv. p. 420.

*Berichte*, 1899, xxxii. 575; 1902, xxxv. 210 and 226.

the more stable, normal isomer. In some cases the electrical conductivity due to the pseudo-isomer ceases at once on the addition of the acid, indicating that the isodynamic change is practically instantaneous; in others the change proceeds more slowly, and can be followed quantitatively from the accompanying changes in electrical conductivity. In all cases the conductivity of the inorganic salt simultaneously formed must, of course, be taken into account. As in the changes of magnetic rotatory power and optical activity, the observable changes in this constitutive property also support the view that they are caused by a reversible isomeric change. The general name of "Pseudo-acids" has been given to the compounds which have not in themselves an acidic structure but are yet able, by intramolecular transformation, to give rise to metallic salts. Similarly, a number of "Pseudo-bases" are known.

*The Solubility.*—The solubility of organic compounds is essentially a constitutive property. The hydrocarbons are, as a rule, very sparingly soluble in hydroxylic solvents such as water or alcohol, but solid hydrocarbons dissolve readily in liquid hydrocarbons. The alcohols, and in general, compounds containing the hydroxyl group, are soluble in hydroxylic solvents but not in hydrocarbons. Solubility is, accordingly, dependent upon the nature of the solvent as well as upon that of the dissolved substance, and similarity in chemical character between the two is always associated with increased solubility. Certain additive relations also occur amongst compounds containing specific groups. For instance, an increase in the number of hydroxyl groups is generally accompanied by increased solubility in water; the ready solubility of the sugars is an example of the influence of a number of hydroxyl groups on this property.

The constitutive character of solubility is evident amongst many other groups of compounds, but it does not in any way afford a method for the differentiation of dynamic isomerides. It has, however, been shown by Lowry<sup>1</sup> that the gradual change in solubility that accom-

<sup>1</sup> Lowry and Robertson, *J. Chem. Soc.*, 1904, lxxxv. 1541; T. M. Lowry, *J. Chem. Soc.*, 1904, lxxxv. 1551; W. Robertson, *J. Chem. Soc.*, 1905, lxxvii. 1298.

panies isomeric change provides a valuable means of determining the proportion of dynamic isomerides in solution. A special importance is attached to this method of ascertaining the proportions of the isomers, because it can be applied even when only one of them can be isolated in the free state.

Each isomer has, like all other compounds, a definite solubility dependent upon the temperature and upon the solvent employed, and after it has been in contact with a solvent for a sufficient time a saturated solution is formed corresponding to its true solubility. If, however, the dissolved substance undergoes isomeric change, a further quantity of the original substance must be dissolved in order to keep the solution saturated, and this quantity will increase proportionately to the extent of the isomeric change. Since the change is reversible, this increase will cease when a condition of equilibrium has been attained, and a saturated solution will again be formed, corresponding to this final solubility. Without entering into the details of the physical relations that exist in this final solution, it will suffice to state that it represents a condition of equilibrium between the dissolved isomers. The ratio of the initial solubility to the final solubility is equal to the ratio of the weight of the original substance to the total weight of material in solution, and thus forms a basis for the calculation of the degree of isomeric change. If, for example, the solubility increases from 1 to 4, it is to be interpreted that the original substance forms approximately one-fourth of the equilibrium mixture in solution.

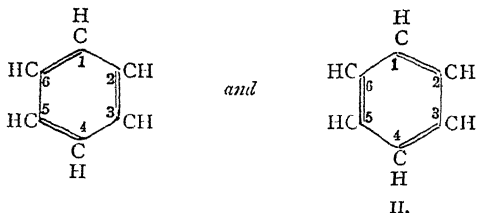
The experimental conditions required in these measurements, in order to obtain accurate results, are somewhat difficult, but the method is one of wide applicability, and has been successfully applied to the study of dynamic isomerism amongst a number of substances, including glucose, galactose, nitro-camphor and  $\pi$ -brom-nitro-camphor. The results are in general accord with the conclusions drawn from the study of other physical properties of these compounds. In the case of glucose, for instance, the equilibrium mixture in methyl alcohol solution corresponds to a mixture of about equal proportions of the  $\alpha$ - and  $\beta$ -oxide forms with, at most, only a very small quantity of the aldehydic isomer. In a solution



containing molecular proportions of ethyl alcohol and water the oxide forms constitute only about 80 per cent. of the total sugar in solution; the remaining 20 per cent. is probably present as a hydrate of the aldehyde form. Measurements by this method are of no value when the solubility is very great, and the observations with glucose cannot, accordingly, be extended to aqueous solutions owing to its excessive solubility in water.

The value of constitutive physical properties for the determination of the structure of compounds is sufficiently evident from the above examples. The relation is in every way both more reliable and more independent than the evidence afforded by chemical reactions, and any changes that these physical properties undergo when they are determined under new conditions are to be interpreted as pointing to a corresponding change in structure. Such changes, effected either by heat or by solution, are therefore regarded as trustworthy evidence of dynamic isomerism.

*The bearing of Dynamic Isomerism on the Structure of Benzene and some of its Derivatives.*—In discussing the relative merits of the Kekulé and centric formulæ for benzene, it was pointed out that a valid objection to the former arises from the theoretical possibility of four, instead of three, isomeric di-substitution products.<sup>1</sup> There is conclusive proof that only three such substitution products can be prepared, and Kekulé sought to bring his formula into accord with this fact by the introduction of dynamic considerations in what is known as the "Kekulé oscillation formula" for benzene. He regarded the positions 1:2 and 1:6 as identical, owing to the oscillation of a double bond between adjacent carbon atoms, as expressed in the following formulæ:—



<sup>1</sup> Cf. Chap. v. p. 72.

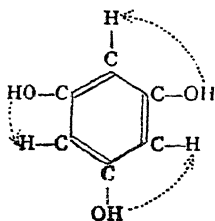
This interpretation he based on the idea that "if two atoms of carbon are linked together by one combining unit of each, they strike against each other once in the unit of time, or in the same time in which monad hydrogen makes a complete vibration. During this time they encounter three other atoms. Carbon atoms, which we call doubly linked, come in contact twice in the unit of time and experience during the same time, two contacts with other atoms."<sup>1</sup> In benzene each carbon atom strikes against two others in the unit of time; once against one and twice against the other, but in the next unit of time this cycle is reversed. In the above formulæ, I. represents the first phase and II. the second phase in the disposal of the carbon affinities; the two formulæ show the position of the bonds uniting the carbon atoms at two different moments of time, which recur alternately. They were not, therefore, intended to represent two differently constructed molecules, but rather two different phases of motion of one and the same molecule.

When the oscillation formula was originally proposed the idea of expressing the properties of compounds by an appeal to isomeric dynamic change had not been developed. Now, Kekulé's view of the oscillation of a double bond is, to some extent, similar to that which is characteristic of isodynamic changes, but with this important difference, that the change in position of the double bond in benzene is not associated with the movement of a hydrogen atom. As in Laar's theory of tautomerism, the mutual change is intramolecular, in contradistinction to the intermolecular change of dynamic isomerides. Beyond the fact that this interpretation of the Kekulé formula suffices to bring it into accord with the isomeric relations of benzenoid compounds, no further proof of its general validity is added. It still fails to express the special stability of benzene, and the fact that the double bonds do not behave as normal ethylene linkings in respect to the addition of halogen acids.

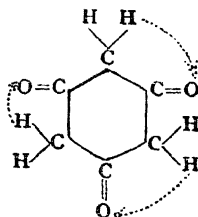
In another direction dynamic isomerism has a direct bearing on the structure of certain benzenoid compounds, which show similar isomeric relations to the ketonic esters; these relations are exemplified by the dihydroxy- and tri-

<sup>1</sup> *Annalen*, 1872, clxii. 86.

hydroxy-derivatives of benzene. No view of the structure of benzene necessitates the same condition of combination of the six CH groups of the nucleus for every derivative of the hydrocarbon. Benzenoid compounds differ in their stability, and this difference is very possibly due to a variation in the structure of the nucleus. Benzene itself probably represents the maximum stability of the ring, and this fact is best expressed by the centric formula for the hydrocarbon. The polyhydroxy-benzenes, on the other hand, appear to represent the minimum stability of the nucleus. They behave as isodynamic compounds, and if their isomeric relations are analogous to those of other hydroxylic substances, they should contain three double bonds in the enolic form. Thus, phloroglucinol, the 1:3:5 trihydroxy-benzene, exhibits a twofold chemical character; it behaves both as a phenol and as a ketone, a difference which is represented in the following formulæ:—



Hydroxylic formula.  
(Trihydroxy-benzene.)



Ketonic formula.  
(Triketo-hexamethylene.)

Phloroglucinol is known only as a well-defined, crystalline compound; its dynamic isomer has not been obtained. Evidence of the structure of the one known form is derived from its selective absorption of ultra-violet light, which, from a comparison with that of its methyl ether and with that of other phenols, indicates that it is essentially hydroxylic in neutral solution;<sup>1</sup> also, its mode of combination with phenyl isocyanate, a reagent which has little or no catalytic action, and which is, accordingly, more reliable than other chemical reagents for the differentiation of dynamic isomers, is in accord with its structure as a

<sup>1</sup> Hartley, Dobbie and Lauder, *J. Chem. Soc.*, 1902, lxxxi. 929; E. P. Hedley, *Ibid.*, 1906, lxxxix. 730.

trihydroxy-benzene.<sup>1</sup> The condition of isomerism in phloroglucinol is, therefore, comparable to that of ethylacetoacetate, and if the movement of the hydrogen atoms in the isomeric changes of the two forms proceeds on similar lines, as indicated by the arrows in the above formulæ, the trihydroxy-compound must have three double bonds and thus accord with the Kekulé, rather than with the centric formula.

The method of Baly and Desch<sup>2</sup> has recently been extended to the study of the isodynamic relations of benzene and its substitution products.<sup>3</sup> The results, so far obtained, show that the ultra-violet absorption spectra of benzenoid compounds, in dilute solution, is likely to prove very helpful in determining the structure of the nucleus in benzene and its derivatives, and in following isodynamic changes amongst aromatic compounds.

<sup>1</sup> Goldschmidt, *Berichte*, 1890, xxiii. 257.

<sup>2</sup> Cf. *ante.*, p. 392.

<sup>3</sup> Cf. *J. Chem. Soc.*, 1905, lxxxvii. 1332, 1347, 1355; 1906, lxxxix. 489, 502, 514, 966, 982; 1907, xci. 426, 1122, 1572.

## CHAPTER XV.

### HETEROCYCLIC AND POLYCYCLIC COMPOUNDS.

Distinction between Isocyclic and Heterocyclic Compounds—The nature of Polycyclic Compounds.

*Heterocyclic Compounds.*—Furfurane and Furfuraldehyde—Pyrrole—Thiophene—Methods employed for the preparation of heterocyclic compounds; Condensation reactions—Antipyrine—Pyridine and Piperidine—The Alkaloids—Conine.

*Polycyclic Compounds with indirectly united rings.*—Triphenylmethane and the triphenylmethane colours—The quinonoid structure of the triphenylmethane dyes—Rosaniline—Aurin—Phenolphthaleïn—Triphenylmethyl.

*Condensed Isocyclic Ring Compounds.*—Naphthalene and Anthracene—The structure of  $\alpha$ -naphthol and of naphthalene—Alizarin; its occurrence as a glucoside—The synthesis of alizarin and the proof of its structure.

*Condensed Ring Compounds, containing an isocyclic and a heterocyclic ring.*—Quinoline and Isoquinoline; their relation to the Cinchona and other alkaloids—Indole and Indigo—The natural occurrence of indigo—The synthetical preparation of indigo.

THE aromatic or benzenoid\* compounds were for a long time the only closed-chain or cyclic compounds known; they belong to the group of "isocyclic compounds," which are characterised by containing closed chains of only carbon atoms.<sup>1</sup> This group is still the most thoroughly studied division of cyclic substances, and much of what is now known of other groups of cyclic compounds is based upon the application of the knowledge derived from the investigation of benzenoid compounds.

Within the last twenty-five years, and especially within the latter half of this period, the preparation and study of other cyclic compounds has been greatly developed. These additions fall into two divisions—the *Heterocyclic* and the

<sup>1</sup> Cf. Chap. iii. p. 38.

*Polycyclic* compounds. The former contain closed chains, which, in contradistinction to those contained in isocyclic compounds, have other atoms in addition to carbon, and they form the third group in the classification of organic compounds;<sup>1</sup> the latter contain two or more closed chains, and according as these are isocyclic or heterocyclic are included in the second or third group in the general classification.

Both divisions comprise substances of theoretical and practical importance, such as thiophene, pyrrole, antipyrine, pyridine, naphthalene, anthracene and alizarin, indole and indigo, quinoline and the natural alkaloids, and the purine group. The reactions concerned in the preparation of the heterocyclic and polycyclic compounds and in the study of their structure and relations are, for the most part, considerably more complex in character than any that have been hitherto considered; also, the two groups include a mass of compounds which it is quite impossible to deal with in any detail in a book of this character. In keeping with the method adopted with other groups of compounds, this chapter will be restricted to some of the salient points concerned with the study of the two divisions, as typified by some of their most important members.

*Heterocyclic Compounds.*<sup>2</sup>—Nitrogen, oxygen, and sulphur are the chief elements which, in combination with carbon, form the closed chains of the heterocyclic compounds. The rings containing five and six atoms are the most stable; some are known containing three, four, and seven atoms, and a few which contain eight or more atoms. Many of these closed-chain compounds are unsaturated, like benzene, and are to be regarded as containing similar potential valencies, which give special stability to their molecules;<sup>3</sup> these, like the benzenoid compounds, add hydrogen by reduction to form alicyclic derivatives.<sup>4</sup> Some heterocyclic, closed-chain compounds are known amongst aliphatic substances, but, as previously pointed out,<sup>5</sup> the chains they contain arise from the presence of

<sup>1</sup> Chap. iii. p. 39.

<sup>2</sup> A full account of the heterocyclic compounds is given in *Heterocyklische Verbindungen*, Wedekind, 1901.

<sup>3</sup> Cf. Chap. v. p. 75.

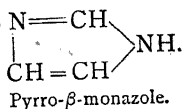
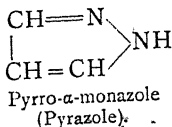
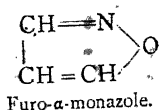
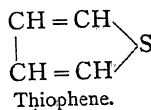
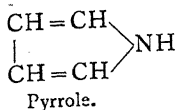
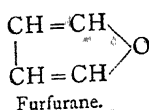
<sup>4</sup> Cf. Chap. v. p. 71.

<sup>5</sup> Cf. Chap. iii. p. 39.

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tly aliphatic  
benzene and its homologues, contain a  
yields a series of derivatives; these  
converted into the simpler closed-chain  
of which is stable and only broken under  
Very few compounds of importance  
or four-membered heterocyclic  
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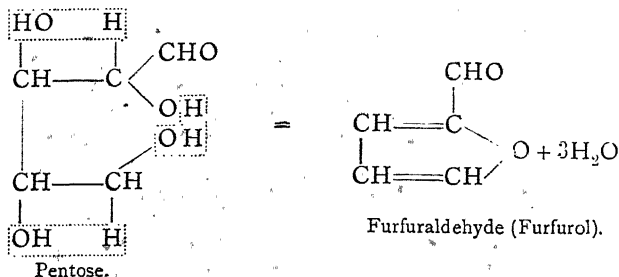


A consideration of the difference in structure between pyrro- $\alpha$ -monazole and pyrro- $\beta$ -monazole shows how different rings may arise amongst heterocyclic compounds by a difference in the relative position of the atoms that form the closed chain; in pyrro- $\alpha$ -monazole the two nitrogen atoms are united directly, in the  $\beta$ -compound they are separated by a carbon atom. This position isomerism is characteristic of all heterocyclic rings, and is the origin of their many varieties; no less than thirty heteratomic rings of this group are now known. The term "azole" is used generically for heteratomic cyclic compounds containing nitrogen.

Furfurane, pyrrole, and thiophene are closely related compounds, the first two of which were known long before the modern methods for the preparation of heterocyclic compounds were developed.

*Furfurane*, which occurs in the distillation products of pine-wood, forms a characteristic aldehyde, known as *furfuraldehyde*, or *furfurol*, which is obtained from all pentoses, the five-carbon atom sugars, by the action of hydrochloric acid. This reaction, which may be repre-

sented by the following equation, is important for both the qualitative and quantitative recognition of pentoses, since the furfural can be easily identified or determined:—



*Pyrrrole* is found in bone-oil, a product obtained by the destructive distillation of bones; owing to the presence of the imido-group, NH, it acts as a weak base. Its tetra-iodo substitution product has been proposed as a substitute for iodoform,<sup>1</sup> under the name of "iodol."

The third of these heteratomic compounds, *Thiophene*, was discovered by Victor Meyer in 1882, in ordinary coal tar benzene.<sup>2</sup> A reaction known as the indophenin reaction had long been employed as a test for benzene; it consists in treating the benzene with isatin (an oxidation product of indigo<sup>1</sup>) and sulphuric acid, when a deep blue coloration is produced. In making this test as a lecture experiment, Meyer failed to obtain the coloration, and ultimately succeeded in tracing his failure to the fact that the benzene he used had not been obtained from coal tar, but from benzoic acid derived from gum benzoin or other natural product. The reaction was at once attributed to the presence of a foreign ingredient in coal tar benzene, which was subsequently isolated by Meyer, and to which he gave the name "*Thiophene*," owing to its containing sulphur and to its close analogy to benzene. It is a mobile liquid, boiling at 84° (benzene boils at 80°.2), and occurs to the extent of about 0.5% in coal tar benzene; it has since been obtained synthetically by several methods, and can now be easily prepared in the laboratory. In its chemical

<sup>1</sup> Cf. Chap. xvi. p. 476.

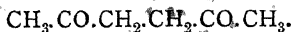
<sup>2</sup> Cf. this chapter, p. 432.

<sup>2</sup> Cf. Chap. vii. p. 112.



character it resembles benzene most closely, yielding substitution products and homologues on similar lines, so that within a few years of its isolation Meyer was able to publish an extensive monograph on the thiophene compounds.<sup>1</sup> It has been found, since the discovery of thiophene, that the presence of this compound has a prejudicial effect upon the coal tar colours made from benzene, and benzene free from thiophene is now prepared for the use of colour manufacturers.

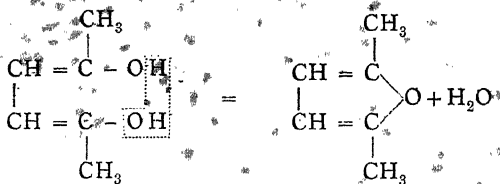
*Methods employed for the preparation of Heterocyclic Compounds.*—Amongst the variety of methods employed for the synthesis of heterocyclic compounds, those by which they are obtained from open-chain or aliphatic substances are of special interest and importance. A reaction which leads on analogous lines to the preparation of homologues of furfurane, pyrrole, and thiophene will illustrate this type of reaction. The starting-point is a double or diketone known as acetonyl acetone; it may be regarded as made up of two acetone radicals and has the formula  $\text{CH}_3\text{CO}\cdot\text{CH}_2\cdot\text{CH}_2\cdot\text{CO}\cdot\text{CH}_3$ . When heated in presence of a dehydrating agent, this compound forms dimethyl furfurane, with ammonia it yields dimethylpyrrole, and with sulphuretted hydrogen (actually by heating with phosphorus pentasulphide) dimethylthiophene is obtained. It is probable that in these changes the diketone functions in its isomeric enolic form<sup>2</sup> as represented in the following equations:—



Acetonyl acetone



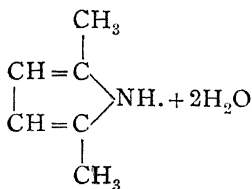
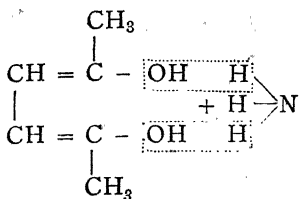
Enolic formula.



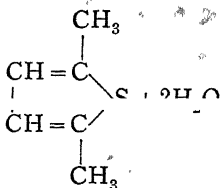
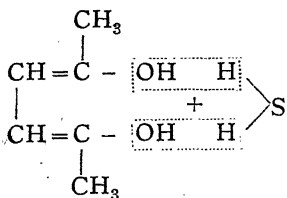
Dimethyl furfurane.

<sup>1</sup> *Die Thiophengruppe*, Victor Meyer, 1888.

<sup>2</sup> Cf. Chap. xiv. p. 368.



Dimethyl pyrrole.



Dimethyl thiophene.

It is to be noted that in each case a closed ring is formed from a chain of four carbon atoms and one other atom, a fact that accords well with the stereochemical relations of the carbon atom as expressed by von Baeyer's tension theory.<sup>1</sup>

Such syntheses are strong evidence in favour of the structure assigned to furfuran, pyrrole, and thiophene; further, they locate the position of substituents, in this instance the methyl groups, and are consequently of value in deciding the orientation of derivatives. These considerations apply generally to heterocyclic as well as to isocyclic compounds.

**Condensation Reactions.**—It will be noticed that in each of the above reactions one or two molecules of water are separated. This separation of water is characteristic of very many of the reactions employed in synthetical organic chemistry, and especially of those that lead to the preparation of more complex from simpler compounds. The process is commonly known as *Condensation*, and although not very accurately defined, its general characteristics are fairly precise. Several examples of the change have already been given; for instance, the preparation of ethane and

<sup>1</sup> Cf. Chap. xii. p. 312.

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isobutane,<sup>1</sup> of ethylacetoacetate,<sup>2</sup> of trimethylene dicarboxylic ester,<sup>3</sup> and that of benzoic acid by the Grignard reaction.<sup>4</sup> These compounds are all to be regarded as *condensation products*; they are formed from their constituents with elimination of water, of alcohol, or of metallic salts such as sodium bromide, and a new combination is effected between the carbon atoms of the reacting molecules.

In some cases the reacting compounds condense quite readily of themselves when heated together and occasionally even at the ordinary temperature, but generally the addition of some reagent is necessary to effect the condensation. A very great variety of compounds are available as condensing agents; some, such as zinc chloride, dry hydrochloric acid gas and acetic anhydride, act directly, either by virtue of their great affinity for water or as catalysts;<sup>5</sup> others, such as metallic sodium, effect the condensation by the elimination of halogen atoms as metallic salts, whilst others again, such as sodium hydroxide and sodium ethylate, act indirectly by the formation of intermediate products, which are usually unstable and are subsequently decomposed with the elimination of water or of alcohol and the formation of the condensation products.<sup>6</sup> Further, with the same reacting substances, one reagent may effect one class of condensation, whilst a second favours another, and this difference applies not only to the possibility of effecting the condensation, but also to the yield of the resulting product, a factor of practical importance.

Condensation reactions are the most important means for obtaining heterocyclic compounds; the preparation of the febrifuge, antipyrine,<sup>7</sup> is a good example of the method.

*Antipyrine* is derived from the five-membered heteroatomic ring, pyro- $\alpha$ -monazole or pyrazole, referred to above. A reduction product of this base is known called pyrazoline; it contains two added hydrogen atoms, forming two  $\text{CH}_2$  groups, and its ketonic derivative,

Cf. Chap. iv. p. 43.

„ ix. p. 179.

„ ix. p. 177.

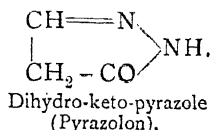
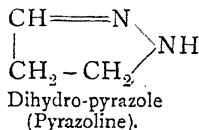
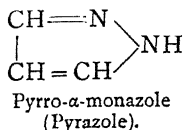
„ xi. p. 253.

Cf. Chap. ix. p. 168.

<sup>6</sup> „ ix. p. 187.

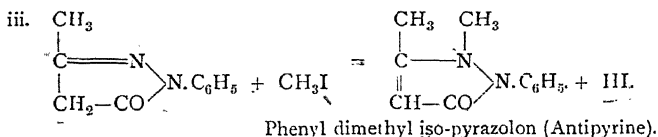
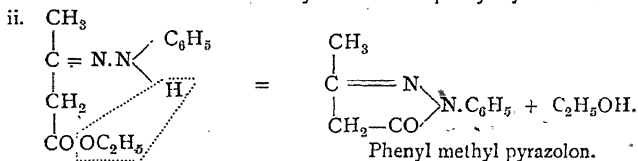
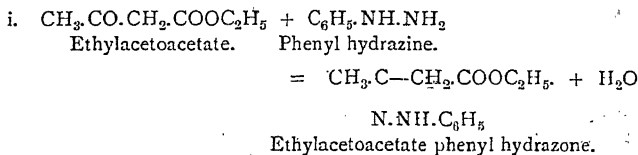
<sup>7</sup> „ xvi. p. 450.

pyrazolon, in which one of these  $\text{CH}_3$  groups is replaced by  $\text{CO}$ , is the mother substance of antipyrine; these relations are shown in the following formulæ:—



The structure and orientation of these three compounds have been satisfactorily established by synthetical reactions.

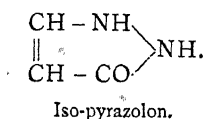
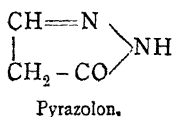
For the preparation of antipyrine, ethylacetoacetate and phenyl hydrazine are heated together and the condensation product formed is converted into antipyrine by the action of methyl iodide, whereby a methyl group is introduced into the molecule. The initial change in these reactions is the formation of a hydrazone between the ketonic group of the ester and phenyl hydrazine,<sup>1</sup> which is, however, very unstable and immediately condenses, with the separation of a molecule of alcohol, to form a pyrazole derivative. These changes are expressed by the following equations:—



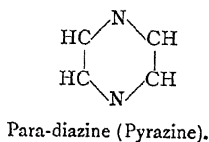
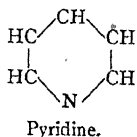
<sup>1</sup> Cf. Chap. xi. p. 261.

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The first and second stages of the preparation are quite straightforward, and the latter shows in an interesting manner the value of a condensation reaction in indicating the orientation of the substituting groups (methyl and phenyl) in the resulting molecule. The introduction of the second methyl group as represented by the third equation involves, it will be seen, an abnormal change and a rearrangement of the linkings in the pyrazolon group. Such molecular changes occur with many pyrazolon derivatives, and caused much confusion in the first attempts to decide their orientation; they are due to the dynamic isomerism of pyrazolon itself, and it is satisfactorily established now that, whilst the direct condensation product of ethylacetoacetate and phenyl hydrazine is a derivative of normal pyrazolon, antipyrine is derived from a pseudo-form, isopyrazolon:—



*Pyridine and Piperidine. The Alkaloids. Conine.*—The six-membered heterocyclic ring compounds show similar variety to the five-membered rings. Those containing one or two atoms of nitrogen are the most important; the latter are known in three isomeric forms corresponding in orientation to the di-substitution products of benzene:—

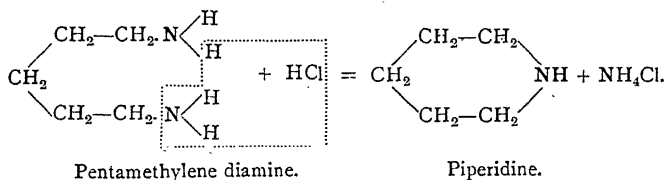


The disposal of the fourth bond of the carbon atoms and of the third bond of the nitrogen atoms is not represented in the above formulæ; these and all similar heterocyclic compounds have undoubtedly potential valencies

akin to those of benzene, but their distribution is at present undecided.

*Pyridine* appears as a benzene ring in which the tervalent group, CH, is replaced by an atom of nitrogen, and this change is the key to its characteristic properties. It is a fairly strong base, forming stable salts, and can give rise to substitution products just like benzene; but it is much more stable, nitric acid, for instance, being unable to attack it. Further, like benzene, it yields hydrides on reduction, compounds of much interest on account of their relation to some of the alkaloids, from which pyridine can be obtained by distillation with solid potassium hydroxide.

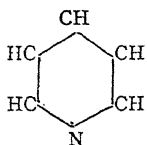
*Piperine*, the alkaloid of pepper, is a salt of the hexahydride of pyridine, called *piperidine*, with a somewhat complex acid, piperic acid. Piperidine can be obtained from and converted into pyridine, and its structure is further shown by a direct synthesis from an aliphatic compound, pentamethylene diamine, the diamino-derivative of pentane, the hydrochloride of which is converted into piperidine by heating, as represented by the equation:—



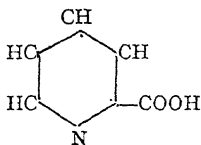
Piperic acid has also been prepared synthetically, and by its combination with piperidine the complete synthesis of piperine has been effected.

*Conine*, the poisonous principle of the hemlock (*Conium maculatum*) is also a pyridine derivative. It was synthetically prepared by Ladenburg (1886), and a special interest is attached to this synthesis on account of its being the first of an optically active alkaloid. The vegetable alkaloids are naturally occurring, complex compounds, characterised by containing nitrogen and by their basic nature. They are seldom found in the free state in plants, being usually in combination with organic acids in the form of salts; they generally have a bitter taste, and many

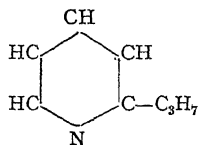
of them are very poisonous. The majority of the alkaloids are crystalline solids and are optically active, usually lævo-rotatory; conine is a liquid and is dextro-rotatory. It has the empirical formula  $C_8H_{17}N$ . Upon oxidation it loses six atoms of hydrogen to form a base conyryne,  $C_8H_{11}N$ , and this forms a mono-carboxylic acid of pyridine (picolinic acid) on oxidation, the carboxyl group of which has been proved to be adjacent to the nitrogen atom of the ring (called the  $\alpha$ -position). Hence, by analogy to the oxidation of the homologues of benzene, the conclusion is justified that conyryne is a pyridine homologue containing one side chain. Pyridine has the formula  $C_5H_5N$ , conyryne  $C_8H_{11}N$ , so that allowing for the replacement of a hydrogen atom in pyridine by the substituting radical, the difference,  $C_3H_7$ , must represent the composition of the latter. This must be either propyl or iso-propyl, and its position in the ring is indicated by the orientation of the acid it forms on oxidation. These relations are shown in the following formulæ:—



Pyridine.

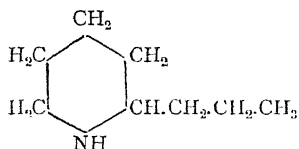


Picolinic acid.

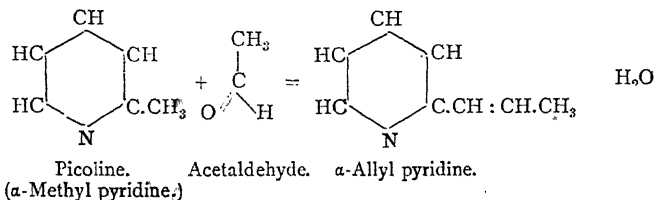


Conyryne.

Conine contains six hydrogen atoms more than conyryne, and, as stated, it forms the latter on oxidation; conyryne is also readily reduced to conine, so the two compounds were regarded as standing exactly in the relation of pyridine to piperidine, a conclusion which has been confirmed by its synthesis and by other reactions. It remained to decide whether the propyl or the isopropyl group was contained in the conyryne and conine molecules. By the oxidation of a conine derivative (benzoyl conine) it has been satisfactorily proved that the  $C_3H_7$  radical is the normal propyl group. The following is, therefore, accepted as the structural formula for conine:—

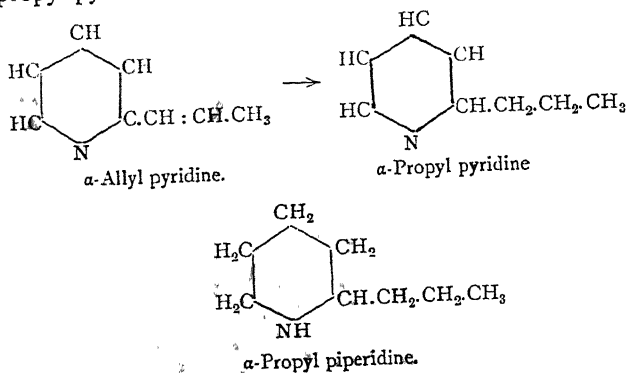

 Conine. ( $\alpha$ -Normal propyl hexahydropyridine.)

The synthesis of such a compound from hexahydro-pyridine (piperidine) by the introduction of a propyl group looks a comparatively simple matter, but owing to a tendency that is often shown by the propyl radical to change to the isopropyl group it could not be effected directly, isopropyl, instead of normal propyl piperidine being obtained by the action of both normal and of isopropyl compounds upon piperidine; the latter is the more stable of the two groups in association with a reduced pyridine ring, thus affording an interesting instance of the dependence of the relative stability of isomeric radicals on the nature of the molecule with which they are in combination. Ladenburg had, therefore, to seek an indirect method to introduce the normal propyl group, and this he effected by reducing allyl pyridine, obtained by the action of acetaldehyde on methyl pyridine (picoline). Picoline can be prepared from pyridine, and its methyl group has been proved to be in the  $\alpha$ -position; acetaldehyde can be obtained from acetylene and by other direct methods of complete synthesis from the constituent elements, whilst pyridine is formed by passing acetylene and hydrocyanic gas through a red-hot tube, and its synthesis *via* piperidine can also be traced back to the direct combination of the elements. Hence, the synthesis of  $\alpha$ -propyl piperidine is complete. The reactions employed by Ladenburg may be represented as follows:—





Upon reduction, the allyl pyridine is first reduced to propyl pyridine and then to propyl piperidine:—



The resulting compound, as in the case of all similar, synthetically prepared, asymmetric substances, was an optically inactive, racemic mixture; by the fractional crystallisation of its salt with dextro-rotatory tartaric acid, the dextro- and laevo-tartrates of conine were separated from which the free bases were obtained by treatment with alkali.<sup>1</sup> The dextro-rotatory compound was, until recently, regarded as identical with the natural product, but subsequent investigations by Ladenburg<sup>2</sup> have shown that although it very closely resembles it in all its properties it differs somewhat in its optical rotatory power. The synthetically prepared compound is accordingly to be regarded as an isomer, to which the name *iso-conine* has been given, but it can be converted into the natural product by heating it to 290° for several hours, so that the complete synthesis of the alkaloid remains established.

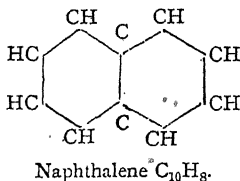
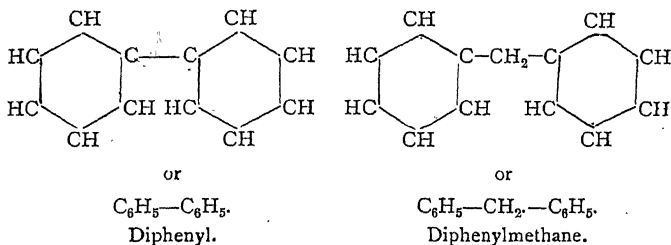
This synthesis has been given in some detail as a type of the method of inquiry that has been adopted in studying the structure of the alkaloids. The majority of the alkaloids are far more complex than conine, and although the structure of most of them is still unknown, very marked advances have been made during recent years

<sup>1</sup> Cf. Chap. xii. p. 295.

<sup>2</sup> *Berichte*, 1906, xxxix. 2486.

in the determination of their constitution and in their synthetical preparation. The method generally adopted for their investigation consists of a hydrolysis followed by a carefully regulated oxidation, processes which, in most cases, ultimately lead to compounds of known structure. It has thus been established that most of the alkaloids are derivatives of the heterocyclic bases, pyridine, pyrrolidine, quinoline, isoquinoline, and purine; of those containing a pyridine ring, the best known are nicotine, atropine, and cocaine, all of which have been synthetically prepared.<sup>1</sup>

*Polycyclic Compounds.*—The cyclic compounds considered up to the present, such as benzene, pyrazole, pyridine, and their derivatives, are characterised by containing one, and only one, ring. The polycyclic compounds include substances the molecules of which are built up of two or more rings, which may be either directly or indirectly united to one another, or which may have carbon atoms common to two or more of the rings which they contain. The following compounds represent these conditions of combination:—



<sup>1</sup> An account of the chemistry of the alkaloids, with particular reference to their constitution, is given in *The Vegetable Alkaloids*, by Pictet; trans. by Biddle, 1904, and in *Die Pflanzenalkaloide*, by J. Brühl, 1900. Cf. also J. B. Cohen, *Organic Chemistry*, 1907, chap. xiv.

In diphenyl the two benzene rings are directly united; in diphenylmethane they are united by a  $\text{CH}_2$  group, or the compound may be regarded as a derivative of methane in which two hydrogen atoms are replaced by two phenyl radicals, whence the nomenclature, diphenylmethane, is derived. Naphthalene is represented as consisting of two benzene rings, having two adjacent carbon atoms in common; molecules of this type are generally called "condensed ring systems," or "condensed cyclic compounds."

The most important of these polycyclic substances are built up of benzene rings—*i.e.*, of six-membered isocyclic rings, or of benzene rings in combination with heterocyclic rings, such as pyrrole and pyridine. A very great variety of these combinations is possible. Speaking generally, the contained rings carry their normal characteristics in respect to their chemical properties and behaviour; compounds containing benzene rings yield substitution, oxidation, and reduction products similarly to benzene, which differ chiefly in their reactivity or in the stability of their derivatives, according to the number and disposition of the contained rings. The polycyclic compounds, such as diphenylmethane, which contain an open chain residue in addition to the rings, represent a similar condition of combination to that of toluene;<sup>1</sup> the aliphatic portion of the molecule remains aliphatic in its chemical character, but certain modifications are induced by the proximity of the benzene rings.

Without entering into the complex classification of polycyclic compounds, which is necessary for their systematic study, the following three important groups will be considered:—

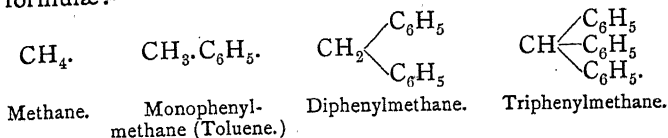
I. *Polycyclic Compounds with indirectly united rings.*—Triphenylmethane and the triphenylmethane colours.

II. *Condensed Isocyclic Ring Compounds.*—Naphthalene, Anthracene, Alizarin.

III. *Condensed Ring Compounds containing an isocyclic and a heterocyclic ring.*—Quinoline, Isoquinoline, Indole, Indigo.

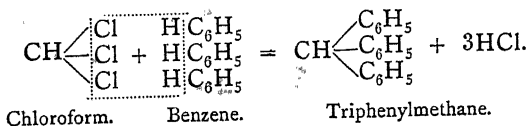
<sup>1</sup> Cf. Chap. viii. p. 127.

I. *Polycyclic Compounds with indirectly united rings.*  
*Triphenylmethane and the Triphenylmethane Colours.*—  
 Diphenylmethane has been given as an example of a polycyclic compound in which two benzene rings are indirectly united; the rings are linked together by the methane residue,  $\text{CH}_2$ . In triphenylmethane a third hydrogen atom of methane is replaced by phenyl; the relation of these compounds to the mono-phenyl derivative, phenylmethane or toluene, is shown in the following formulæ:—



*Triphenylmethane* is the mother hydrocarbon of the rosaniline, eosin, and other important dyes, which although replaced to a considerable extent to-day by the faster azo-colours, offer some useful points of study in respect to the relation of structure to colour,<sup>1</sup> in addition to their historical interest as the representatives of the earliest developments of the aniline colour industry.

The structure of triphenylmethane is proved by its synthesis from benzene and chloroform which is effected by the action of aluminium chloride (Friedel and Crafts' reaction<sup>2</sup>), according to the following equation:—



The three phenyl groups of triphenylmethane retain all the characteristic properties of a benzenoid hydrocarbon; the methane residue which unites them similarly retains its aliphatic character, but the associated electro-negative

<sup>1</sup> An account of the relation of the structure of compounds to colour is given in a monograph by H. Kaufmann, "Ueber den Zusammenhang zwischen Farbe und Constitution bei chemischen Verbindungen," *Sammlung chem.-und chem.-technischer Vorträge*, 1904.

<sup>2</sup> Cf. Chap. xi. p. 238.

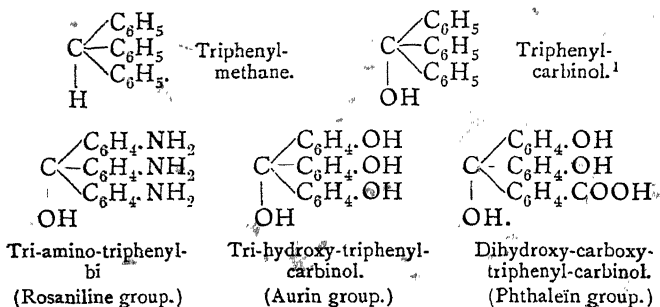
phenyl groups increase the reactivity of the hydrogen atom of the CH group, especially in respect to the ease with which it can be oxidised, with the formation of hydroxylic compounds, known as *carbinols*. These carbinols are the direct mother substances of the triphenylmethane colours; the colours arise by the replacement of hydrogen atoms in the phenyl radicals by salt-forming groups. Three important series of colours are thus derived:—

I. *The Malachite green and Rosaniline group* which contain the amino-group,  $\text{NH}_2$ .

II. *The Aurin group*, which contains the hydroxyl-group, OH.

III. *The Phthaleïn group*, which contains both hydroxyl and carboxyl groups.

The simplest relations of these compounds are shown in the following formulæ:—



None of the colours of this group has been found in nature; they are all made by synthetical processes, in which the amines, phenols, and aldehydes of benzene and its homologues are the most important initial products.

Perkin's "Mauve," discovered in 1856, and the first of the aniline colours that was manufactured, was obtained by the oxidation of aniline sulphate, and "Fuchsine," so called from the similarity of its colour to that of the fuchsia, was got by the oxidation of a mixture of aniline

<sup>1</sup> *Carbinol* is the name given to methyl alcohol, the simplest of all alcohols; thus *triphenyl-carbinol* is methyl alcohol in which three hydrogen atoms are replaced by phenyl groups.

and its homologues, known commercially as "aniline oil," in 1859. The course of these oxidations and the structure of the resulting compounds were not determined till some twenty years later (1876-78), when Emil and Otto Fischer<sup>1</sup> established their relation to triphenylmethane and prepared para-rosaniline,<sup>2</sup> one of the constituents of fuchsine, directly from the hydrocarbon.

By the action of nitric acid upon triphenylmethane the trinitro-compound,  $\text{CH}(\text{C}_6\text{H}_4\text{NO}_2)_3$ , is obtained, which yields triaminotriphenylmethane,  $\text{CH}(\text{C}_6\text{H}_4\text{NH}_2)_3$  on reduction. The methine group,  $\text{CH}$ , is readily oxidised, as stated above, with the formation of triaminotriphenylcarbinol  $\text{C.OH}(\text{C}_6\text{H}_4\text{NH}_2)_3$ , which is the mother-substance or "base" of para-rosaniline. Fuchsine is a mixture of para-rosaniline and its methyl homologue, rosaniline. The dyes are the salts of the triamino-carbinols, but none of the carbinols of this group are dyes in the free state. The structure of these salts has been the subject of much controversy, and there is still a considerable difference of opinion as to their constitution. A special interest is attached to this problem as it bears not only on the specific structure of the salts of triphenylmethane derivatives but upon the wider and more fundamental question of the relation of the colour and dyeing properties of benzenoid compounds to their chemical structure. In describing the relation of the azo-dyes<sup>3</sup> to the compounds from which they are derived, it was pointed out that certain radicals (chromophores) and salt-forming groups (auxochromic groups) are always present in the substances which possess dyeing properties; this relation holds amongst the triphenylmethane compounds, and the discussion of the nature of the carbinol salts is concerned with establishing a more definite view of the structure of chromophore groups.

In 1889 Nietzki suggested that the triphenylmethane dyes are derivatives of a di-ketone of benzene known as quinone, and of its imido-compounds, and this view, which was subsequently extended by Armstrong to all

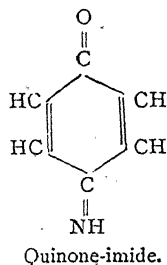
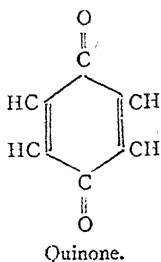
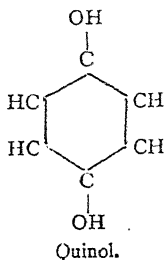
<sup>1</sup> *Berichte*, 1876, ix. 891; *Annalen*, 1878, cxciv. 242.

<sup>2</sup> The prefix "para" does not refer to the orientation of the dye, but was originally applied to the compound because para-toluidine was used in its preparation.

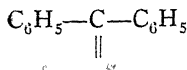
<sup>3</sup> Chap. x. p. 208.

coloured benzenoid compounds, has now been very generally accepted; it is usually termed the "quinonoid" structure.

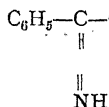
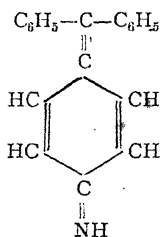
To make these relations clear the structure of quinone and of quinone-imide may first be regarded, as also their relation to quinol, para-dihydroxybenzene, from which quinone is readily obtained by oxidation:—



It is to be noted that in quinone and in quinone-imide, which latter was isolated for the first time a few years ago,<sup>1</sup> the para-carbon atoms are linked by a double bond to oxygen and to the divalent, imido-group, NH, respectively. If now the oxygen of quinone-imide be replaced by the diphenyl-methylene group,



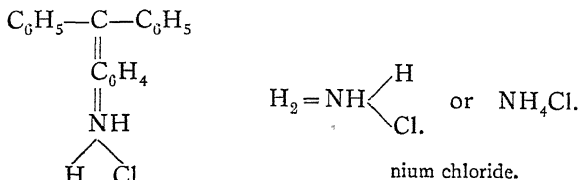
a compound of the following structure will result:—



Diphenylmethane quinone-imide or Imido-triphenyl methane.

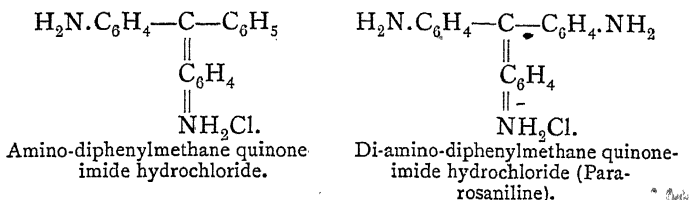
<sup>1</sup> Willstätter and Mayer, *Berichte*, 1904, xxxvii. 1494.

which will give rise to a hydrochloride and other salts by the tervalent nitrogen atom becoming quinquevalent, just as ammonium chloride results from ammonia:—

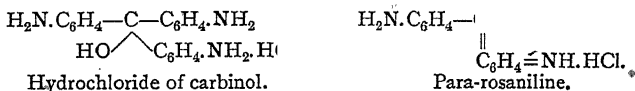
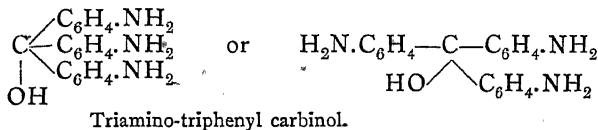


Imido-triphenylmethane hydrochloride.

This structure of imido-triphenylmethane represents the *chromogen* of the rosaniline group of colours. Compounds of this type have been isolated by von Baeyer and Villiger.<sup>1</sup> By the introduction of the salt forming or auxochromic amino-groups the dyes result:—



It remains to indicate the relation of these formulæ to that of the carbinol of the rosaniline group given above. This, by the addition of acid to one of the amino-groups first forms a salt of the carbinol, which then loses a molecule of water and passes into the quinonoid form, as shown in the following formula:—

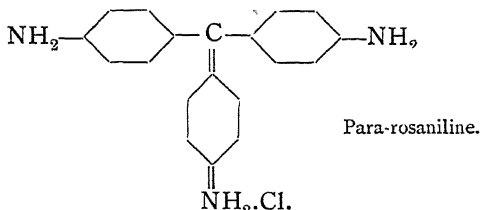


<sup>1</sup> *Berichte*, 1902, xxxv. 1189, and subsequent papers.





the number and nature of the basic groups present, and in all cases those compounds only are dyes in which these groups are in the para-position to the methane carbon; in para-rosaniline, for instance, all the three amino-groups are in this position, a fact which has been established in part by converting it into, and in part by preparing it from, compounds of known orientation:—



The triphenylcarbinol salts, containing only one amino-group, are orange yellow in colour, and possess feeble dyeing properties. When a second amino-group is present the resulting compound is a dye of a violet colour, but of little tinctorial value. A third amino-group leads to the red dye, para-rosaniline. By substituting the hydrogen atoms of the amino-groups by methyl the diamino-compounds yield green, the rosaniline compounds violet dyes, the tinctorial powers of which increase with the number of methyl groups present; the tetra-methyl compound of the former is the important dye, *Malachite green*. If the phenyl radical be introduced into the amino-groups of rosaniline instead of methyl, blue dyes are formed, of which *aniline blue*, the triphenyl derivative, is a valuable and much-used colour. The modifying influence of other radicals, such as ethyl and benzyl, as also of halogens, nitro-groups, sulphonic acid groups, etc., on the colour of the dyes of this group has been thoroughly worked out, so that it is now possible, in great measure, to foretell the changes such substituents will induce. The influence of the simultaneous presence of two or more chromophores has also been determined.

The structure and relations of the other two groups of triphenylmethane colours referred to above, the aurins and the phthaleïns, have been studied on very similar lines. They also contain a quinonoid chromogen, which results



possibility that the formation of the colour is due to a change in structure accompanied by ionisation, and from this standpoint the above quinonoid formula for the sodium salt is to be accepted as satisfactory.

Phenolphthaleïn is of no tinctorial value, but it is largely used as an indicator in the titration of acids and alkalis, since the smallest excess of alkali converts the colourless compound into its bright red salt. The most important dyes in the phthaleïn group contain halogen substituents, and include eosin, erythrosin, galleïn, and a closely allied group of colours known as rhodamines; they are nearly all red, crimson, or scarlet dyes, and are characterised by great brilliancy of colour.

Much interest has been aroused recently by the discovery of a compound which reacts in many ways as if it had the formula  $(C_6H_5)_3\equiv C-$ <sup>1</sup>, i.e. *Triphenylmethyl*. This is the only instance known in which carbon appears to be tervalent, and the evidence upon which the above structure rests has naturally been subjected to a searching criticism. Unfortunately the molecular weight of the compound is unknown, and it is thus possible that it may be a hexaphenyl ethane.<sup>2</sup> The chief argument for the presence of a free carbon linking is the great ease with which the compound adds on chlorine, etc., and even atmospheric oxygen. Two forms of triphenylmethyl are known, which are probably dynamic isomers, but further work is needed before its structure can be regarded as established.

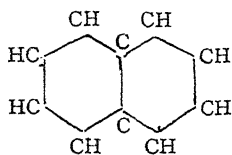
II. *Condensed Isocyclic Ring Compounds. Naphthalene. Anthracene. Alizarin.*—Naphthalene and anthracene are both important constituents of coal tar;<sup>3</sup> they are the initial products for the preparation of many valuable dyes of which azo-colours, indigo and alizarin, are the most prominent. In chemical structure they belong to the "condensed ring systems" of the polycyclic compounds, both containing isocyclic rings of six carbon atoms—i.e., benzene rings. Naphthalene is built up of two such rings,

<sup>1</sup> Gomberg, *Berichte*, 1900, xxxiii. 3150.

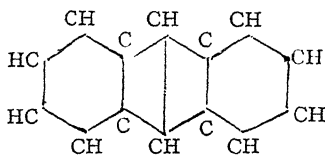
<sup>2</sup> Cf. Tschitschibabin, *J. prakt. Chem.*, 1906 [2], lxxiv. 340; *Berichte*, 1907, xl. 3965; 1908, xli. 2421; Gomberg and Cone, *Berichte*, 1906, xxxix. 1461, 3274; Hantzsch, *Berichte*, 1906, xxxix. 2478; Gomberg, *Berichte*, 1907, xl. 1847.

<sup>3</sup> Cf. Chap. vii., p. 113.

anthracene of three; in the former the two rings have two carbon atoms in common, in the latter there are two pairs of carbon atoms united in this manner, conditions of combination which are represented by the following structural formulæ:—



Naphthalene.  $C_{10}H_8$ .



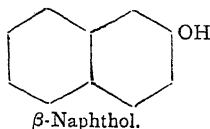
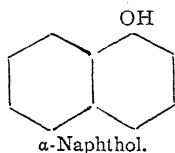
Anthracene.  $C_{14}H_{10}$

The correctness of these formulæ has been fully established by a variety of syntheses, details of which are to be found in the text-books on organic chemistry. Both hydrocarbons are crystalline solids melting at  $79^\circ$  and  $213^\circ$ , respectively; naphthalene is isolated from the carbolic oil of coal tar by removing the associated phenols by treatment with alkali, whilst anthracene, which is found in the anthracene oil, the last distillate of coal tar, together with many other complex hydrocarbons, is obtained in a sufficient degree of purity for the manufacture of alizarin by treatment with suitable solvents and subsequent volatilisation by steam.

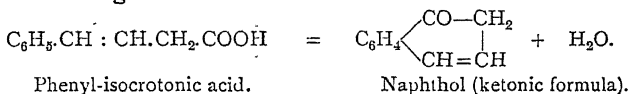
The isomeric relations of these compounds are, owing to their polycyclic character, considerably more complex than those of benzene. According to the above formula, naphthalene should give rise to two mono-substitution products, and to ten di-substitution products, and this conclusion has been proved to be correct by the preparation of this number of derivatives. The orientation of naphthalene and anthracene derivatives is decided by methods similar to those employed in the case of benzenoid compounds, but owing to the more complex relations the problem is considerably more difficult, especially when two or more different substituents are present.

The mono-substitution products of naphthalene are known as  $\alpha$  and  $\beta$ , according as the substituent is attached to the carbon atom next to one of those which is common to the two benzene rings, or is separated from the latter by an intermediate carbon atom, as shown in the following

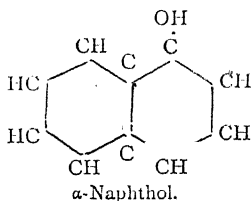
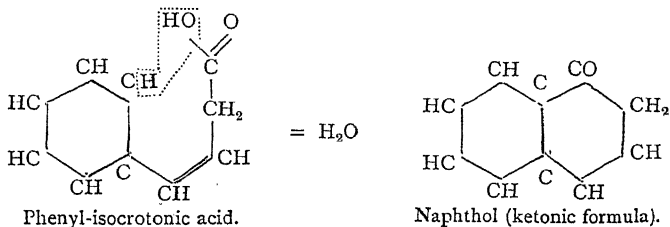
formulae for the hydroxy-naphthalenes or naphthols, the analogues of the phenols:—



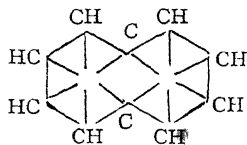
It is obviously fundamental to have means of deciding which of any two substitution products of naphthalene has the substituent at the α- or β- position. A simple synthesis, of α-naphthol will illustrate this. The phenyl derivative of an unsaturated aliphatic acid, isocrotonic acid, separates a molecule of water when heated and forms one of the naphthols; the change, which is shown in the following equations, is most simply represented as taking place *via* an alternative ketonic formula for naphthol, as an intermediate stage:—



or:—



This synthesis has several points of interest. In the first place it is clear that the hydroxy-group is attached to a carbon atom next to one of those common to the two rings, and that it is, therefore, in the  $\alpha$ -position. The compound formed is a solid which melts at  $94^\circ$  and which gives a violet coloration with ferric chloride, properties which consequently are to be accepted as characteristic of  $\alpha$ -naphthol. Consistently with theory only one isomer is known, which melts at  $122^\circ$  and which is coloured green by ferric chloride; this is necessarily the  $\beta$ -compound. Secondly, the synthesis points clearly to the naphthalene ring being built up by the combination of two benzene rings with two adjacent carbon atoms in common. And finally, the double bond present in phenyl-isocrotonic acid is only represented in the ketonic formula for  $\alpha$ -naphthol, not in the normal formula, which is in accord with all its properties and chemical character. The full representation of the carbon linkings in this compound, as in naphthalene and its derivatives generally, necessitates the presence of further potential or other linkings. The nature of the latter has been the subject of much experimental study, especially in connection with certain reduction products of the naphthols and of the amino-derivatives of naphthalene, the naphthylamines, and there is considerable evidence in favour of accepting the following centric formula, proposed by Bamberger, as the best representation of the conditions of linking in the naphthalene molecule:—



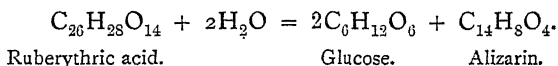
Centric formula for Naphthalene (Bamberger).

The derivatives of naphthalene that are so largely employed in the colour industry consist chiefly of the naphthols, the naphthylamines and their sulphonic acids, for the preparation of which the hydrocarbon is the starting point. The naphthylamines, like their analogue aniline, can be diazotised, and by the combination of these diazo-compounds of naphthalene with the amines

and phenols of both benzenoid and naphthalene hydrocarbons numerous important azo-dyes are prepared.<sup>1</sup>

*Alizarin*.—The successful establishment of the aniline colour industry, which had been accomplished within some twelve years after the discovery of Perkin's "mauve" in 1856, was due essentially to the synthetical preparation of the rosaniline dyes. These and their derivatives formed the bulk of the artificial colours which had entered into competition with natural colouring matters. None of the latter had then been prepared artificially, but in 1868, alizarin, the colouring matter of the madder root, one of the most valuable dyes, was obtained synthetically by Gräbe and Liebermann, and the following year both Perkin and Caro succeeded in preparing it on a commercial scale.

The alizarin, or madder dye, well known in the form of "turkey red," is found in nature in the root of the madder (*Rubia tinctorum*) and other plants of the Rubiaceæ family. It occurs in the form of a glucoside<sup>2</sup> known as ruberythric acid; its decomposition into glucose and alizarin is represented by the equation:—



Another colouring matter, known as purpurin, is found side by side with alizarin in madder, and various preparations of these products were formerly made, such as garancin and madder-flowers.

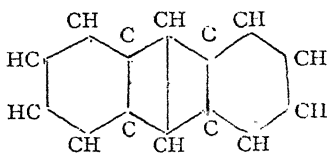
The discovery that led to the synthetical preparation of alizarin was that upon distilling it over red-hot zinc dust it yielded the hydrocarbon anthracene.<sup>3</sup> Anthracene was known to give a compound called anthraquinone upon oxidation and by introducing two hydroxyl-groups into the latter, Gräbe and Liebermann effected the synthesis of alizarin; the method they adopted was subsequently modified for manufacturing purposes. The relations of these three compounds are shown in the following formulæ:—

<sup>1</sup> Cf. Chap. x., p. 211.

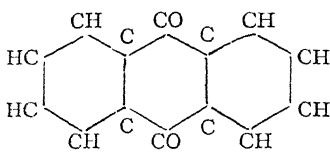
<sup>2</sup> „ xiii, p. 346.

<sup>3</sup> Cf. Chap. xi., p. 267.

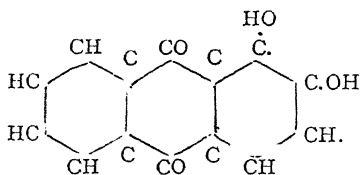




Anthracene.



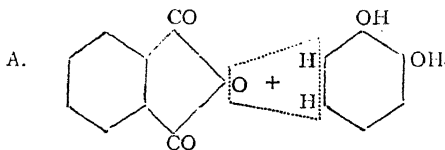
Anthraquinone.



Alizarin (Dihydroxy-anthraquinone).

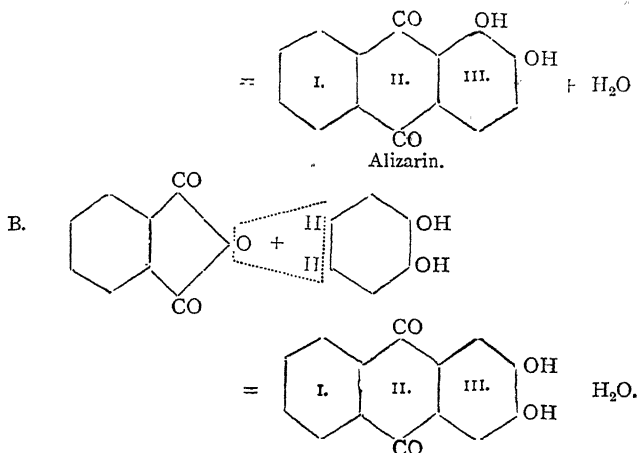
The formula of anthraquinone as a di-ketone of anthracene has been fully established by synthetical reactions, and that of alizarin as a dihydroxy-anthraquinone has been similarly proved. In connection with the latter, the determination of the position of the two hydroxyl-groups is of importance, and this has been effected in the following way.

The anhydride of phthalic acid, the ortho-dicarboxylic acid of benzene, yields alizarin when heated with catechol (ortho-dihydroxy-benzene) in presence of a dehydrating agent. Since the two hydroxyl groups in catechol are adjacent, there are two, and only two, possible positions that the pair can occupy in relation to the two carbon atoms that are common to the second (II.) and third (III.) benzene rings of the alizarin molecule, as will be clear from the following equations:—



Phthalic anhydride.

Catechol.



To decide between these positions, monohydroxy-benzene (phenol) was employed instead of catechol in this synthesis, when it was found that two different monohydroxy-anthraquinones were formed, each of which was converted into alizarin by replacing a second hydrogen atom in ring III. by hydroxyl. Now, if either of the two hydroxyl groups in the formula for alizarin given in equation B were eliminated, the monohydroxy-anthraquinones formed would be identical, because each of these two groups is similarly situated to ring II.; they both occupy the  $\beta$ -position of the naphthalene ring.<sup>1</sup> The positions given in equation A, however, are different; they correspond to the  $\alpha$ - and  $\beta$ -positions of the naphthalene substituents respectively, and since phenol yields two distinct monohydroxy-anthraquinones, one must have the hydroxyl group in the  $\alpha$ -position, whilst in the other this group must occupy the  $\beta$ -position. Finally, since both yield the same compound, alizarin, when a second hydroxyl group is introduced, the proof is complete that the latter has these substituents in the positions represented in equation A.

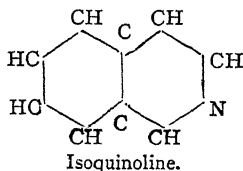
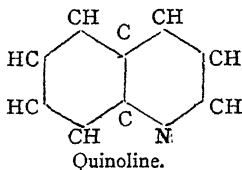
There are several important dyes closely related to alizarin, all of which are hydroxy-anthraquinones, and which contain more than two hydroxyl groups; in all of

<sup>1</sup> Cf. this chapter, p. 424.

these, two of the contained hydroxyl groups have the same orientation as those of alizarin. Compounds in which no two hydroxyl groups occupy these positions are not dyes, so that the orientation of the compound, in addition to its composition, appears as an essential factor in respect to its tinctorial properties, as in the case of the rosaniline dyes.

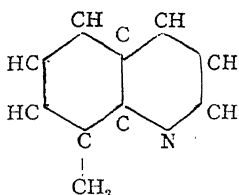
Alizarin itself is of a brilliant red colour, but it is insoluble in water, and only its salts act as dyes. The alkali salts are soluble, those of the heavy metals insoluble and of very varying colour, from bright red to violet and brown; it is the latter that are used in dyeing, and they are precipitated on the fabric by "mordanting" with suitable salts of iron, aluminium, chromium, etc., which are decomposed by heating, in presence of alizarin, with the formation of the corresponding insoluble alizarin salts. By simple precipitation of the alkali salts of alizarin with salts of iron, aluminium, and other metals, similar insoluble salts are prepared for use as pigments, which are known as "lakes."

III. *Condensed Ring Compounds containing an Isocyclic and of a Heterocyclic ring. Quinoline. Isoquinoline. Indole and Indigo.*—The condition of combination between benzene rings that gives rise to the condensed polycyclic compounds naphthalene and anthracene can also obtain between one or more isocyclic and heterocyclic rings. The most important of such mixed, condensed polycyclic compounds are those containing nitrogen; a considerable variety of such compounds is known, owing to the possibility of isomeric relations similar to those referred to in connection with the azole rings.<sup>1</sup> Two compounds, for instance, are known consisting of a benzene ring united to a pyridine ring with two carbon atoms in common; they are called quinoline and isoquinoline, and have been proved to h.....

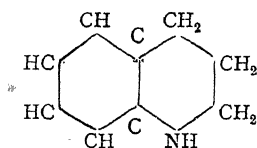


<sup>1</sup> Cf. this chapter, p. 402.

Both compounds are analogous in structure to naphthalene, but owing to the presence of the nitrogen atom they resemble pyridine in possessing basic properties; in stability they stand midway between benzene and pyridine, as would be expected from their structure. Owing to the near relation of quinoline to several important alkaloids, a special interest has attached to the study of its derivatives, which have accordingly been very thoroughly investigated. By the replacement of a hydrogen atom by a methyl group the methyl-quinolines are obtained of which no less than seven isomers are possible. All of these seven methyl-quinolines are known, as are also the seven quinoline carboxylic acids which result from them by oxidation. Many other substituting groups can be introduced into the quinoline molecule, and upon reduction, these derivatives, as well as quinoline itself, yield characteristic reduction products, the most important of which contain four added hydrogen atoms in the pyridine ring. The following are the formulæ of ortho-methylquinoline and of quinoline tetrahydride:—



Ortho-methylquinoline.



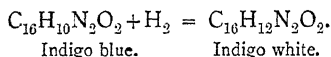
Tetrahydroquinoline.

The important alkaloids of the cinchona bark, quinine and cinchonine, are converted by a number of reagents into simple quinoline derivatives, and the quinoline ring undoubtedly constitutes a part of their complex molecules; the remainder of their structure still awaits elucidation. The presence of an isoquinoline ring in the alkaloids papaverine, narcotine, hydrastine, and berberine has also been satisfactorily established.

*Indole and Indigo.*—Indigo blue is the chief colouring matter of the Indigo plant (*Indigofera tinctoria*); it also occurs in other species of *Indigofera* as well as in European woad (*Isatis tinctoria*). It is a dark blue solid, character-

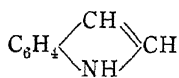
ised by its marked insolubility in all ordinary reagents; it sublimes on heating, giving off a fiery red vapour, and its vapour density corresponds to the molecular formula  $C_{16}H_{10}N_2O_2$ .

The application of indigo in dyeing and printing cannot be effected directly, owing to its insolubility. The method adopted is to reduce it to a colourless compound known as indigo white, which is soluble in alkalis, and which is readily taken up by the treated fibre; on exposure to air the indigo white is oxidised to indigo blue, which thus becomes fixed on the fabric. This reduction, which can be effected by a variety of reagents, corresponds to the addition of two atoms of hydrogen, as represented in the equation:—

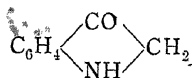


The first complete synthesis of indigo was effected by von Baeyer in 1878; the method employed was purely of scientific interest, but two years later the same chemist discovered a further method for its preparation which gave promise of successful working on a manufacturing scale. This achievement was the outcome of many years of work on the structure of indigo and of a number of compounds which stand in close relation to it. Three compounds—indole, indoxyl, and isatin—are of special interest and importance in connection with these investigations.

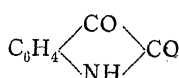
Indole yields indigo when oxidised by ozone; indoxyl is very readily oxidised to indigo by exposure to air in presence of alkalis, and isatin, which is itself obtained by the oxidation of indigo, is converted into the dye by reducing agents. The structure of these compounds is shown in the following formulæ:—



Indole or Benzo-pyrrole.

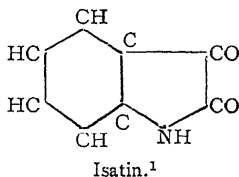
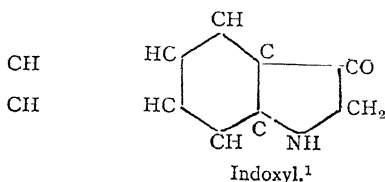
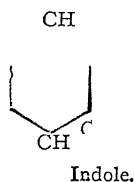


Indoxyl.

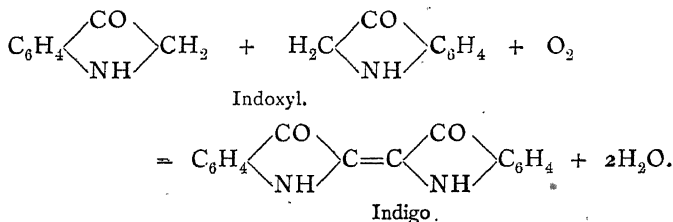


Isatin.

or:—



All are polycyclic compounds of the condensed type, indole, which is to be regarded as the parent compound of the other two, being built up of a benzene ring in combination with a pyrrole ring,<sup>2</sup> with two adjacent carbon atoms common to the two rings; hence its nomenclature benzo-pyrrole. The structural formula of indigo itself is based upon the structure of these and related compounds; it consists of two indoxyl rings united by a double linking between two of the carbon atoms, and its formation by the oxidation of indoxyl is represented by the following equation:—



The relations of indoxyl and isatin to indigo, which were established by von Baeyer and his pupils, form the

2.—The formulæ given here are those of pseudo-indoxyl and of pseudo-isatin, as they give a simpler expression of the relation of these compounds to indigo and to the synthetical reactions described later, than the normal formulæ for these compounds. (Cf. Chap. xiv. p. 361.)

<sup>2</sup> Cf. this chapter, p. 402.

basis for the most important synthetical methods for the preparation of the dye, whilst the relation of indoxyl to indigo has a direct bearing on the conditions under which the dye is obtained from the indigo plant.

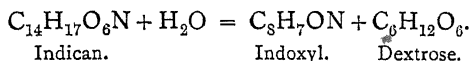
*The natural occurrence of Indigo.*—The general method adopted for obtaining indigo from the plant is to cut the plants off close to the ground when they are about three months old and shortly before they flower. After cropping, the plants are again allowed to grow until they are sufficiently mature to admit of a second cutting. Occasionally a third and even a fourth crop is made, but each of these successive crops yields less blue and that of poorer quality than the previous one. The cut plants are placed in large stone cisterns called "steepers," where they are covered with water and kept in position by means of boards and heavy stones; the water, which is run off when the steeping is completed, is then agitated by beating with wooden paddles, when the indigo is separated in blue flocks, which are collected, pressed, cut into cubical blocks and dried. More scientific methods for the culture of the indigo plant and the extraction of the dye are now being studied, the necessity for improvement having been forced upon planters since synthetical indigo was placed on the market. By due attention to the use of artificial manuring, principally with superphosphates, an increased plant production of from 50 to 100 per cent. is said to have been obtained. Further, it is now suggested that since the chief content of the colouring matter is in the leaves, these only should be stripped and steeped, instead of cutting the plants down as hitherto. Also, the old beating process is regarded as wasteful, and a method is now being used in which air is blown in at the bottom of the vats through a series of perforated pipes; it is claimed that this alteration increases the yield of indigo by from 23 to 30 per cent. The necessity of the steeping process has also been called into question; it is known that a bacterial fermentation takes place at this stage, but how far this is favourable to or inimical to the yield of indigo is by no means decided.<sup>1</sup>

The recognition of the best method to be adopted for

<sup>1</sup> Cf. "The cultivation, manufacture and uses of Indigo," C. Rawson, *J. Soc. Chem. Ind.*, 1899 xviii. 467; *J. Soc. of Arts*, 1900, xlviii. 413.

the extraction of indigo from the plant and also of the most favourable conditions of culture necessary to produce plants rich in the dye have, until recently, been prevented by the previously incomplete knowledge of the chemical nature of the compound in which it is initially present in the plant and also by the absence of reliable methods for its analytical determination.

It was originally thought that the colouring matter occurred in the plant in the form of the soluble reduction product indigo white, and this view was held until Schunck (1855) showed that it was present as a glucoside, called *Indican*, which he regarded as a compound of indigo with a sugar, indiglucin, into which components it was hydrolysed by the action of enzymes. Subsequent investigations by Hoogewerff and ter Meulen,<sup>1</sup> which have since been extended and confirmed by A. G. Perkin and W. P. Bloxam,<sup>2</sup> have shown, however, that indican is not a glucoside of indigo itself, but of indoxyl, which is decomposed by hydrolysis in accordance with the following equation; the sugar obtained is ordinary grape-sugar or dextrose:—



This is, therefore, to be regarded as the initial decomposition which takes place in the "steepers." Indoxyl, as stated above, is readily oxidised to indigo, and the formation of the latter from the plant extract is accordingly dependent upon the oxidation brought about by the air. From this explanation of the mechanism of the formation of the indigo it is readily seen that the modification of blowing air through the liquid extract from the plants may play an important part in the production of the dye. Indeed, Perkin and Bloxam<sup>3</sup> have shown that if indican be hydrolysed in absence of air the indoxyl is not converted to indigo, but to a brown amorphous substance, of no tinctorial value, resembling indigo brown. From this it appears that indigo brown is also a derivative of indoxyl; it is formed as a by-product in the manufacture of indigo

<sup>1</sup> Cf. *J. Soc. Chem. Ind.*, 1900, xix. 1100.

<sup>3</sup> *Loc. cit.*

<sup>2</sup> *J. Chem. Soc.*, 1907, xci. 1715.



from the plant. In order to improve the yield of indigo it would thus appear necessary to regulate the oxidation which takes place during the steeping in such a way as to produce the maximum quantity of indigo, and to minimise such secondary reactions as the above. This might be attained by modifying the conditions of the blowing process or by the addition of suitable oxidising agents, or possibly of catalysts.

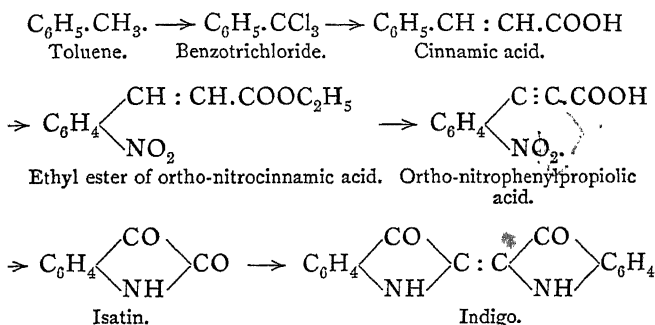
With the more accurate knowledge which is now available, as the result of these investigations, as to the nature of indican and with the reliable methods now known for its estimation,<sup>1</sup> it should prove possible to greatly improve the methods for the culture and extraction of indigo. Meanwhile the competition between the natural and the synthetical product has become acute, and the best aid of science will be needed to stay the speedy relegation of the former to the position of an extinct industry. In 1906, synthetic indigo had so far superseded the natural product that of a total weight of 46,683 cwt. of indigo imported into Great Britain only 7,641 cwt. were from the indigo plant; taking into consideration the proportion of pure indigo contained in the natural product, this represents only between 8 and 9 per cent. of the total import.

*The synthetical preparation of Indigo.*—There are three compounds that have served as starting points for the chief methods at present known for the synthetical preparation of indigo:—benzene, toluene and naphthalene. All three are important constituents of coal tar and are largely employed in the manufacture of coal tar colours. The relative commercial values of the methods for the manufacture of indigo are, naturally, largely dependent upon the initial product chosen, for in view of the fact that the total annual consumption of indigo amounts to about 5000 tons it is obvious that that method of manufacture is favoured for which there is a sufficient supply of the initial material without necessitating the simultaneous production of an unmarketable quantity of other products. Of the three raw materials mentioned, naphthalene is most

<sup>1</sup> Cf. Gaunt, Thomas and Bloxam, *J. Soc. Chem. Ind.*, 1907, xxvi. 1174; also, Bergthell and Briggs,<sup>2</sup> *ibid.*, 1907, xxvi. 1172; and *Report to the Government of India*, by W. P. Bloxam, 1908.

favoured in this respect; neither benzene nor toluene are available in sufficient quantity for the manufacture of the total indigo required by any one of the processes at present known, especially in view of the demand for these hydrocarbons for other purposes, as, for instance, for the manufacture of explosives. Still it is quite possible that new conditions of manufacture may alter these relations.

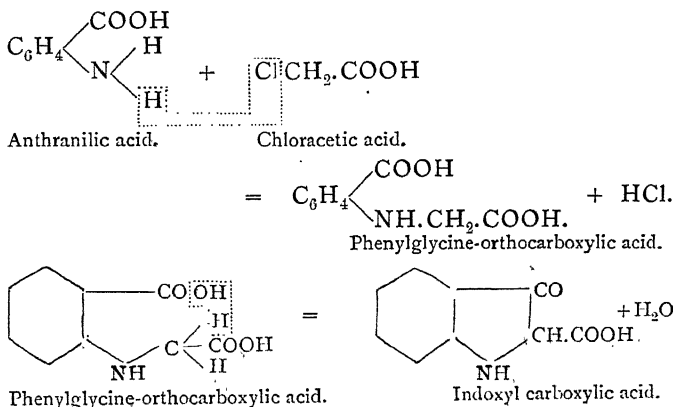
In von Baeyer's original synthesis toluene was the starting point, from which he prepared cinnamic acid; from this he obtained the ethyl ester of ortho-nitrocinnamic acid which he then converted into a doubly unsaturated acid, ortho-nitrophenyl-propionic acid. This last compound yields indigo when treated with reducing agents, and since the method supplied a means for producing the dye on the fabric, by first treating the latter with a solution of a salt of the acid and then applying the reducing agent, it promised most hopefully. It did not, however, prove a commercial success, the cost of production being too great in comparison with the price of natural indigo. The chemical changes in the process, which are outlined below, are somewhat complicated; an isatin derivative is an intermediate product in the final reduction:—



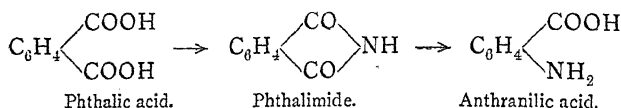
Of the methods that are now in use or have been proposed for the manufacture of indigo, three are of special importance; there are, however, many more known, each of which has contributed its quota of knowledge and scientific interest to the study of the



In this equation the separation of the molecule of water that results in the formation of indoxyl, is represented as taking place between the hydrogen atom next to, or in the ortho-position to the NH group of the benzene ring and the OH of the carboxyl group. This must be the condition of condensation for indoxyl to be formed, because the two carbon atoms that are common to the contained rings are in the ortho-position to one another. An ortho-condensation is similarly necessary for the preparation of isatin or of indigo from any benzenoid compound, and it will obviously be favoured by starting from an ortho-derivative of benzene or a homologue, instead of leaving it to chance, as in the above synthesis from phenyl glycine. The selection of suitable ortho-compounds has, in consequence, played an all important part in the methods for the preparation of indigo. This consideration led to the substitution of the ortho-carboxylic acid of aniline (anthranilic acid) for aniline, by Heumann, with the result that a greatly improved yield of indigo was obtained. By the action of chloracetic acid on anthranilic acid, the ortho-carboxylic acid of phenylglycine is formed, which when fused with alkali and subsequently oxidised yields indigo, a carboxylic acid of indoxyl being formed as an intermediate product. The stages in this synthesis are represented by the following equations:—



The difficulty in this process, from a commercial stand-point, was the manufacture of the anthranilic acid. It has been overcome by starting its preparation from naphthalene which is oxidised to phthalic acid, from which an imide (phthalimide) is prepared which can be directly converted into anthranilic acid :—



The way in which the successive stages of this synthesis have been made practical working processes is a remarkable story of the combination of the highest scientific knowledge with the greatest practical skill and resource, and it is not too much to say that it stands without parallel amongst the modern achievements of chemical industry.<sup>1</sup>

<sup>1</sup> Cf. "The Synthesis of Indigo," Meldola, *J. Soc. of Arts*, 1901, p. 397. "Zur Geschichte der Indigosynthese," von Baeyer, *Berichte*, 1900, xxxiii., Appendix, p. 51. Brunck, *Berichte*, 1900, xxxiii., Appendix, p. 71.

## CHAPTER XVI.

### THE SYNTHESIS OF PHYSIOLOGICALLY ACTIVE ORGANIC COMPOUNDS.

The preparation of pure drugs from natural products—The investigation of the physiological action of drugs—Grouping of synthetically prepared drugs as antipyretics, narcotics and antiseptics.

*Antipyretics.*—Quinine and Cinchonine—Quinoline compounds—Antipyrine—The general chemical character of metabolic changes; oxidation, reduction and combination—Antipyretics derived from Aniline—Acetanilide—Exalgine—Phenacetine—Lactophenine—Phenocoll.

*Narcotics.*—Hypnotics and anæsthetics—The alcohols—Amylene hydrate—Halogen compounds—Aldehydes—Chloral hydrate. Urethane, Chloralamide, Hedonal—Ketones, Sulphonal—Veronal—Local anæsthetics:—Cocaine.

*Antiseptics.*—Phenol and its homologues—Iodoform and “iodoform substitutes”—Salicylic acid—Salol and the “Salol principle”—Aspirin—Guaiacol.

*Other Synthetically prepared drugs.*—Solvents for Uric Acid:—Piperazine, Lysidine — Purgatives: — Anthrapurpurin, Phenolphthalein.

*The relation between taste and chemical structure;* Saccharine, Dulcin.

THE association of the science of organic chemistry with that branch of the art of healing which is concerned with the preparation and use of drugs dates from the early years of last century, when quinine, cinchonine, brucine, strychnine and other vegetable alkaloids were isolated from their natural sources. The preparation of these alkaloids in a pure state supplied the material for the accurate study of their individual physiological actions, and thus the empiricism previously associated with the use of the drugs of which they were the essential constituents was removed.

The value of the bark of the cinchona tree as an antipyretic has been known since the middle of the seventeenth century; more than twenty alkaloids are present in this product in addition to quinine, whilst the percentage of the latter varies in different barks from 2 to 13. To have access to a pure product, in place of the varying mixtures formerly in use, has been an important gain to medicine; some of the alkaloids associated with quinine differ from it both qualitatively and quantitatively in their physiological effect, and, therefore, their presence in the crude drug prevented that guarantee of reliability which is now associated with the pure alkaloid.

With the development of the analytical and synthetical methods of organic chemistry attempts were naturally made to prepare these more valuable vegetable alkaloids in the laboratory, an achievement which has not yet been effected; but the study of their structure has led to the recognition of the presence of certain groups in their molecules which, on the assumption that compounds having a similar chemical constitution should have a similar physiological action, supplied the first step towards the synthetical preparation of physiologically active compounds.

Quinoline derivatives had been obtained from quinine and cinchonine, and this fact led Otto Fischer and Filehne (1882) to the study of the physiological action of quinoline compounds, in the hope of preparing substances of value as antipyretics; the discovery of *Kairine* and the recognition of the therapeutic value of *Antipyrine* followed as a result of these investigations. Researches by Crum Brown and Frazer (1869) on the influence of certain groups, such as methyl and ethyl, on the physiological action of brucine, strychnine and other alkaloids were amongst the earliest attempts to trace a relationship between chemical structure and physiological action, and by the application of their method of inquiry to compounds of known constitution the study of this subject has advanced with remarkable rapidity.

The vegetable alkaloids have thus been the starting point for the study of the synthetical preparation of physiologically active compounds; there is little doubt that the present knowledge of the physiological relations

of organic compounds must serve as an important aid in the synthesis of these valuable natural products, and in this manner pharmacology and therapeutics may repay their debt to the science of organic chemistry.

The study of the physiological action of synthetically prepared organic compounds has now become thorough and systematic. Certain typical groups have been recognised as possessing specific narcotic, antiseptic or antipyretic actions, whilst the modifications in these effects produced by the introduction of substituting groups are fairly accurately known. The knowledge of the relation of chemical structure to physiological action is, however, still very incomplete, and many new groups of compounds, possessing valuable therapeutic properties, have been prepared during the past few years, the physiological action of which was, in no way, anticipated.

"Pharmaco-therapeutics," as this subject is sometimes termed, forms the youngest development of modern organic chemistry, both from a scientific as well as from an industrial standpoint, whilst in its application to medicine it has proved an advance of real value in the means for combating sickness and disease.

From the scientific side the study of the physiological action of synthetically prepared compounds, followed by inquiry into the relation between the structure of organic compounds and their physiological effect, has led to an important extension of the scope of chemical physiology and to a closer association of the borderland work of the chemist and physiologist.

The manufacture of compounds of therapeutic value such as antipyrine, phenacetine, salol, sulphonal, and veronal, has developed to an industry of commercial importance, as may be judged by the fact that the value of these products imported into England is well over £250,000 annually. This manufacture is chiefly carried out at the German colour works, where the initial materials and well-staffed laboratories have provided most favourable conditions for its development.

The aim of the present chapter is to show, by means of some of the best investigated instances, along what lines chemical synthesis has advanced in the preparation of physiologically active compounds.



*The Investigation of the Physiological Action of Drugs.*—

As a preliminary consideration it is well to bear in mind that whilst the preparation by the chemist of new compounds of possible therapeutic value is a comparatively easy task, the investigation of the action of drugs by the physiologist is a much more difficult form of experimental inquiry. The complexity of the animal body, the many functions it exercises, the innumerable and mutually dependent processes which take place in it, are all factors which contribute to the difficulty of investigation. These difficulties are not so much in regard to the tracing of any final effect a drug may produce, but in correctly attributing its action to the function or process by which the observed result has been attained.

How a drug acts and where it acts are problems in the study of pharmaco-therapeutics that concern the physiologist, but it may not be out of place to refer to some of the simpler causes that may condition or complicate the physiological action of a drug.

The physiologist distinguishes between the direct and the indirect action of a drug. For instance, curare kills by paralysing the ends of the motor nerves; this is its direct action. But, under certain circumstances, death is preceded by convulsions due to a secondary or indirect effect. Again, a drug may exert a local action on that part of the body with which it first comes into contact, which may give rise to symptoms in other, remote parts of the body of an unfavourable character. Such secondary effects occur in the action of quinoline as an antipyretic and are of such a nature as to prevent its application in practice. Many intestinal antiseptics have an injurious effect on the stomach, and hence has arisen the preparation of such compounds as salol and guaiacol carbonate, which are carried through the stomach unchanged, thus avoiding the local irritant action which stands apart from the real value of the drug.

The effect of a drug varies also with the quantity. Atropine, for example, in small doses slows the pulse; in larger quantities it quickens the beating, and in very large quantities again slows it. Small doses of naphthalene increase the blood pressure, large doses decrease it; and paraformaldehyde in doses of 3-4 grams acts as a purga-

tive, whilst smaller quantities cause constipation. These variations arise from the fact that different tissues are affected according to the quantity of the drug administered; the effect of a substance on one and the same tissue does not vary with the dose. Further, the quantity of a drug required to produce a certain result is no absolute value. What has to be considered is the quantity of the drug acting, and this is related to the weight of the body acted upon, to the rapidity with which the drug is absorbed in the system, and the proportion this bears to the rapidity of excretion. Hence, the mode of administration of a drug causes variations in the physiological effect produced; kairine and antipyrine, for instance, have a much greater effect when injected subcutaneously than when taken into the stomach by the mouth. The solubility or insolubility of a drug may be favourable or unfavourable to its use, and it is especially to be borne in mind that the therapeutic value of this factor does not rest with the conditions of solubility outside the body, but with those which obtain with the various juices, fats, and oils which are concerned with the general animal metabolism.

The different actions of a drug in health and in disease have also to be considered. Quinine can reduce the temperature  $3^{\circ}$  to  $4^{\circ}$  in cases of fever, but under normal conditions its antipyretic action is very slight. Similarly, salicylic acid and its salts are valuable antipyretics in cases of acute articular rheumatism, but they have no such action in health, and but little effect in most other febrile conditions.

Such are a few among the many points the physiologist has to consider in assigning to a drug what is called its "action," and they have to be carefully weighed in considering the relations that have been traced between the chemical structure and the physiological effect of drugs.<sup>1</sup>

<sup>1</sup> Literature on synthetically prepared drugs and on the relation of physiological action to chemical structure:—

✓ Lauder Brunton. *An Introduction to Modern Therapeutics*, 1892.  
Croonian Lectures, 1889.

Lauder Brunton. *The Action of Medicines*, 1897.

B. Fischer. *Die neueren Arzneimittel*, 1894.

S. Fränkel. *Die Arzneimittel-Synthese*. Second edition, 1906.

F. Francis and J. Fortescue-Brickdale. *The Chemical Basis of Pharmacology*, 1908.

W. F. Loebisch. *Die neueren Arzneimittel*, 1895.

Most of the synthetically prepared drugs can be conveniently grouped under the three headings of:—

1. *Antipyretics.*
2. *Narcotics.*
3. *Antiseptics.*

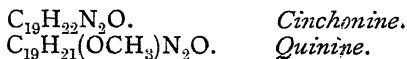
The properties of some assign them to more than one of these groups, but these will be dealt with in the sequel under the heading which embraces their most important therapeutic applications. There are, in addition, a few drugs of interest which fall outside these groups, which will be dealt with separately, as:—

#### 4. *Other Synthetically prepared Drugs.*

##### I. ANTIPYRETICS.

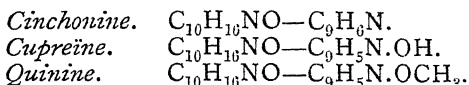
The influence of alkyl groups on the physiological action of alkaloids was, as already stated, first studied by Crum Brown and Frazer, and their investigations, associated with the still incomplete knowledge of the structure of these compounds, gave the first impetus to the synthetical preparation of antipyretics.

*Quinine and Cinchonine.*—Quinine has long been known as a valuable antipyretic, and as a specific against malaria and other intermittent fevers. The alkaloid cinchonine, which is associated with quinine in cinchona bark, is far less certain in its action than quinine, and it must be administered in much greater doses in order to exert an antipyretic effect. Chemically these two compounds are very closely related; they differ only by the presence of a methoxy-group ( $\text{OCH}_3$ ), in quinine in place of a hydrogen atom of cinchonine.



From reliable decompositions these compounds undergo there is little doubt but that both contain a quinoline ring, and that their difference is due to the substitution of a hydrogen atom in this ring by methoxyl. An alkaloid *cupreine* is known which chemically stands midway between cinchonine and quinine; it contains a quinoline

ring, with a hydrogen atom replaced by hydroxyl. The relations of these three compounds are shown in the formulæ:—



The group,  $\text{C}_9\text{H}_6\text{N}$ , represents the quinoline ring, which is attached by one bond to the rest of the molecule,  $\text{C}_{10}\text{H}_{16}\text{NO}$ , the structure of which is not yet known.

The difference in structure between quinine and cinchonine is so small that it seems out of all proportion to the difference in their physiological effects. Cupreïne, like cinchonine, has only a slight antipyretic action, and since it is likely that the effect of the latter is due to its being partially oxidised to cupreïne in the body, the difference in the physiological action of quinine and cinchonine becomes even more marked. By substituting the hydrogen of the hydroxyl-group of cupreïne by methyl, quinine is obtained, and other groups, such as ethyl, propyl, or amyl, can be similarly introduced to form homologues of quinine. All these compounds possess the antipyretic and specific actions of quinine; they are, in fact, more powerful febrifuges than quinine itself, but considerably more toxic. Hence, the physiological action of quinine cannot be attributed simply to the methyl group, but it is obviously closely associated with an alkylated hydroxyl group attached to a quinoline ring.

*Quinoline Compounds.*—The recognition of the fact that the quinoline ring forms an essential portion of the quinine molecule led to attempts to prepare febrifuges from quinoline and from the allied bases, isoquinoline and pyridine; the influence of alkyl groups in modifying the physiological action of the alkaloids gave useful direction to these attempts. Quinoline itself possesses powerful antiseptic and antipyretic properties, but it causes so many unpleasant secondary reactions in the system, culminating in collapse, that it is of no practical therapeutic value. By substituting a hydrogen atom by hydroxyl, a hydroxyquinoline (para) can be obtained, but both this compound and its methyl-ether have a much weaker antipyretic action than quinoline, and, in addition, they have a tendency to

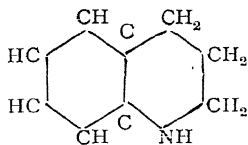
decompose albumin, which is prejudicial to their use. The relation of these compounds is exactly that of cinchonine to cupreine and quinine, so that the successive replacement of a hydrogen atom in quinoline by hydroxyl and methoxyl produces an opposite physiological change to that which occurs with cinchonine:—

<i>Quinoline.</i>	$C_9H_7N.$
<i>Hydroxy-quinoline.</i>	$C_9H_6N.OH.$
<i>Methoxy-quinoline.</i>	$C_9H_6N.OCH_3.$

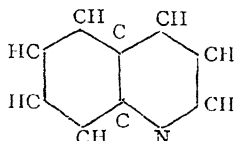
The relative position of the methoxy-group, both in this last compound and in quinine, to the nitrogen of the quinoline ring, is the same (para), so that there is nothing in the orientation of the group to account for the difference in its effect on the physiological action of the two mother substances, quinoline and cinchonine. Hence, although the antipyretic action of quinine is closely associated with the presence of the methoxy-group in the contained quinoline ring, other portions of the molecule must be contributory to this effect. The function of the methoxy-quinoline group may be to supply the special atomic grouping which is necessary to bring the quinine molecule into reaction with the tissues, the specific action of the alkaloid being due to other portions of the molecule. Although the structure of these other portions is not yet decided, there is evidence that they include a reduced pyridine ring, which is probably responsible for the antipyretic, if not for the specific action of the alkaloid. For it was shown long ago by McKendrick and Dewar (1873) that the hydrides of heterocyclic bases possess a more powerful physiological effect than the simple bases, a fact that has been confirmed by Filehne and Otto Fischer, in the studies that led them to the preparation of kairine, the first important synthetically prepared antipyretic.

Tetrahydroquinoline<sup>1</sup> is more toxic than quinoline, and this greater physiological effect is to be largely attributed to the presence of the NH or imido-group, which physiologically, as well as chemically, is very reactive:—

<sup>1</sup> Cf. Chap. xv. p. 431.

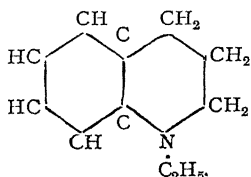
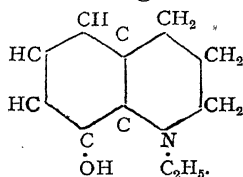
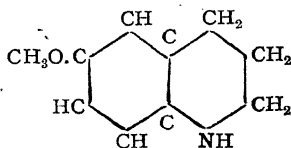


Tetrahydroquinoline.



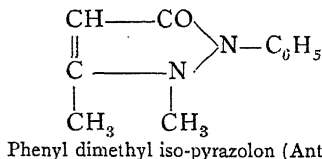
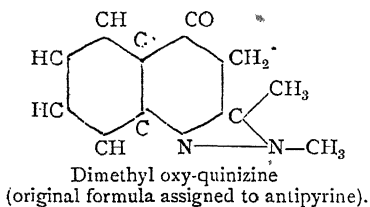
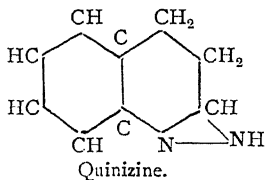
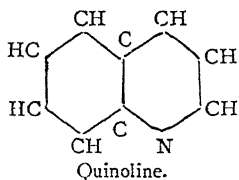
Quinoline.

This reactivity led to the replacement of the hydrogen of the imido-group by an alkyl, with the object of giving increased stability to the molecule; the resulting methyl and ethyl compounds were prepared as antipyretics under the name *Kairoline*. *Kairine* contains an additional hydroxyl group which causes the antipyretic effect to take place more quickly. *Thalline* is a third hydroquinoline febrifuge, the tetrahydride of paramethoxy-quinoline, the reduction product of the quinoline group present in quinine, but which, it is to be remembered, is not hydrogenised in the latter. These three compounds have valuable antipyretic properties, but they give rise to unpleasant and dangerous secondary effects. The hydrochloride of kairine was tried in practice for a time and with some success, but it proved too unreliable to admit of any extended use. The chief interest in these compounds centres in what they have taught; meanwhile it is important to note that, although antipyretics, none of them possess the specific action of quinine against intermittent fevers.\* Their chemical relations are shown in the following formulæ:—


 Kairoline (Tetrahydro-*n*-ethyl quinoline).

 Kairine (Ortho-hydroxy-tetrahydro *n*-ethyl quinoline).


Thalline (Para-methoxy-tetrahydroquinoline).

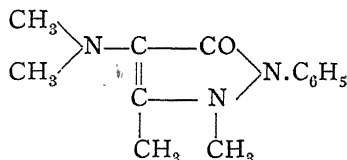
The discovery of the therapeutic properties of *Antipyrine* has proved to be the most valuable, as well as the first outcome of the teachings of the earlier synthetically prepared febrifuges. Antipyrine was prepared by Knorr in 1884. He at first regarded it as the derivative of a hypothetical base, quinizine, and as such it bore sufficient analogy to the physiologically active quinoline compounds described above to suggest the study of its physiological action. Subsequent investigations have led Knorr to assign to it a different structural formula; it has been proved to be a substituted pyrazolon,<sup>1</sup> but it was its supposed relation to kairine that first led to the examination of its physiological effect. These structural relations are shown in the following formulæ:—



The practical value of antipyrine is too well known to require comment. Its antipyretic action is nearly free from injurious secondary effects; it is rapidly absorbed by the system and slowly eliminated, thus standing in marked

<sup>1</sup> Cf. Chap. xv. p. 406.

contrast to thalline and kairine, since the former of these is absorbed slowly and eliminated slowly, whilst the latter is eliminated rapidly, although slowly absorbed. Like both these quinoline derivatives, antipyrine does not possess the specific action of quinine against malaria. It has, however, other therapeutic effects, especially as an anti-neuralgic, which have very greatly contributed to its medicinal value. The commercial success that has attended the discovery of the physiological value of antipyrine has led to the preparation of numerous derivatives and allied compounds which share its antipyretic action, the majority of which, however, do not approach it either in general reliability or utility. In fact only one, a compound in which a hydrogen atom in antipyrine is replaced by the group  $N(CH_3)_2$ , is in any way comparable with it in this respect. This substance, which has been introduced under the name of *Pyramidon*, is three times as powerful in its action as antipyrine, and possesses the advantage of acting more gradually and for a longer time:—



Dimethyl-amino-antipyrine (Pyramidon).

Both in pyramidon and in antipyrine a methyl group is attached to a nitrogen atom. This group is essential to their physiological effects, for the compound which differs from antipyrine only by its absence has no antipyretic action whatever. As in the case of quinine, however, this group serves more probably as a point of contact or "anchor" with the tissues than as the carrier of the physiological effect. The more recent study of the relation of chemical structure to physiological action has throughout been to show that the influence of specific radicals or groups depends upon the nature of the molecules with which they are associated, rather than upon their intrinsic composition, as was formerly thought to be the case.

*The general Chemical character of Metabolic changes:—Oxidation, Reduction, and Combination.*—A large number

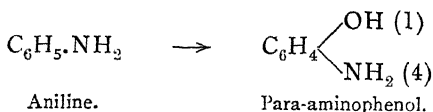


of antipyretics have been prepared, derived from aniline and from other aromatic bases, of which phenacetine and acetanilide (antifebrine) are the best known.

The study of the changes that aniline and its derivatives undergo in their passage through the system has played an important part in the recognition of the therapeutic value of these compounds, and it will be useful, as a preliminary, to consider the general chemical nature of such metabolic changes.

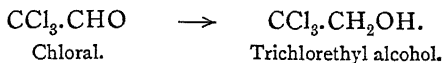
The chemical changes that take place in the animal body, as far as the normal constituents of food are concerned, result essentially in the formation of the typical oxidation products—carbon dioxide, water and urea.<sup>1</sup> When drugs, which are to be regarded as abnormal or foreign constituents of the animal economy, are introduced into the system, the general function of these same chemical processes is to convert them into non-poisonous or less poisonous products, a change which is effected either by oxidation, by reduction, or by chemical combination.

Amongst oxidation products formed during the passage of such foreign substances through the body, acids and hydroxylic compounds are the most important. Thus, methyl alcohol and its esters yield formic acid, benzaldehyde, benzoic acid; in other cases more complete oxidation results, as is shown by the conversion of oxalic acid into carbon dioxide and water, and of homologues of acetamide into urea. Aromatic compounds are, as would be expected, more stable towards the oxidation changes of the system than aliphatic substances. In a few instances complete oxidation occurs; the more interesting changes are those which result in the introduction of an hydroxy group. Benzene is oxidised to phenol, and aniline is partially converted into para-aminophenol; this introduction of a hydroxy-group in the para-position is characteristic of the change undergone by many other aromatic compounds;—



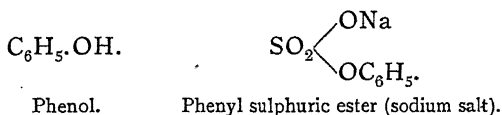
<sup>1</sup> Cf. Chap. x. p. 218.

Reduction processes are less common, but a number of examples of this change are known. Chloral hydrate is partially eliminated as trichlorethyl alcohol, and the nitro-group in some aromatic compounds is reduced to the amino-group.



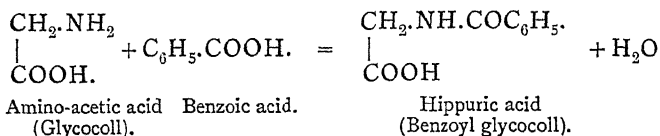
Such oxidation and reduction processes are generally followed by chemical combination. The chief combinations are those with sulphuric acid, glycocholic acid, glycuronic acid, the acetyl group and sulphur.

Phenol, and the dihydroxy-derivatives of benzene and their homologues, when taken internally, are eliminated in combination with sulphuric acid, derived from the oxidation of the sulphur contained in the albumin, as ethereal salts; phenol, for instance, as the sodium salt of phenyl sulphuric ester. The solubility of such salts aids their elimination in the urine, but the more important point is that they are not poisonous; a dose of 30 grams of the sodium salt of phenyl sulphuric ester is without any toxic action.

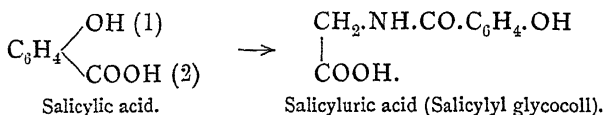


Glycocholic or amino-acetic acid, which occurs in the body in combination with certain bile acids and which is a characteristic decomposition product of proteins, combines not only with benzoic acid,<sup>1</sup> but also with its homologues, substitution products and such substances as are converted into any of these by the oxidation processes of metabolism; the products of combination are eliminated as complex acids or their salts, of which hippuric acid (benzoyl glycocholic) is the simplest example. This combination also results in the formation of compounds of decreased toxicity:—

<sup>1</sup> Cf. Chap. x. p. 219.



Similarly, salicylic acid is eliminated as salicyluric acid (salicyl-glycocoll):—



It is of interest to note, however, that when the acid radical of aromatic compounds is converted into the corresponding amide or ethereal salt the elimination takes place in combination with sulphuric acid and not with glycocoll; this has been shown to be the case when salicylamide or methyl salicylate (gaultheria oil) is administered.

Glycuronic acid is a metabolic product of considerable physiological importance. Chemically it is closely allied to the sugars, being the aldehyde of one of the saccharic acids,<sup>1</sup> from which it can be obtained by reduction.

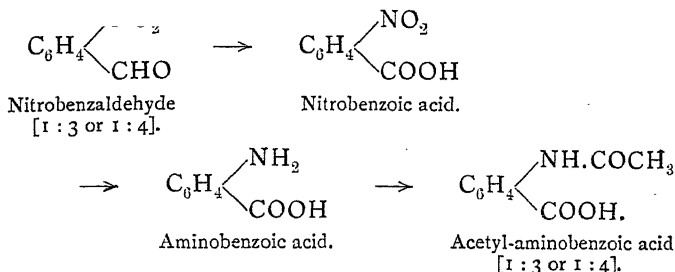


Combination with this acid, with the formation of complex glucoside-like compounds, occurs after the administration of such compounds as aliphatic aldehydes, alcohols and ketones, of aromatic hydrocarbons, nitrobenzene, camphor and morphine. Amongst the aldehydes, chloral and butyl-chloral are included, and the elimination of glycuronic acid in the urine is also a characteristic of chloroform narcosis. Further, many phenols, after combination with sulphuric acid, combine further with glycuronic acid before being eliminated.

The formation of acetyl derivatives in the body is a comparatively rare occurrence, but great interest attaches

<sup>1</sup> Cf. Chap. xiii. p. 338.

to the change since the introduction of an acetyl group is one of the most frequent methods adopted to decrease the toxicity of drugs. As an example of this change, the result of the administration of meta- or para-nitrobenzaldehyde may be cited;<sup>1</sup> acetyl-amino-benzoic acid is formed, so that the metabolic changes include the oxidation of the aldehyde group to carboxyl, the reduction of the nitro- to the amino-group, and the subsequent acetylation of the latter:—



An important decrease in toxicity accompanies the combination of certain cyanogen compounds with sulphur, a change that takes place in the body after the administration of acetonitrile and of its more poisonous homologues, the nitriles of propionic and butyric acid. The CN group is converted into the thiocyanogen group, CNS. Some such combination may be the basis of the interesting action which sodium thiosulphate exerts as an antidote to cyanogen and other double or di-nitriles of the oxalic series of acids.<sup>2</sup>

In addition to these metabolic processes, specific chemical changes may be effected as compounds pass through the body, by the substances with which they come into contact. The most important of these occur in the stomach and in the duodenum. The gastric juice of the stomach consists essentially of a saline solution of pepsin containing a little (0.2 per cent.) free hydrochloric acid. This free acid can act as a solvent for bases, and has the power of decomposing certain acetyl compounds, such as lactophenine;

<sup>1</sup> Cf. R. Cohn, *Z. physiolog. Chem.*, 1892, xvii. 274.

<sup>2</sup> Cf. Heymans and Masoin, *Archives de Pharmacodynamie*, 1896, iii. 77.

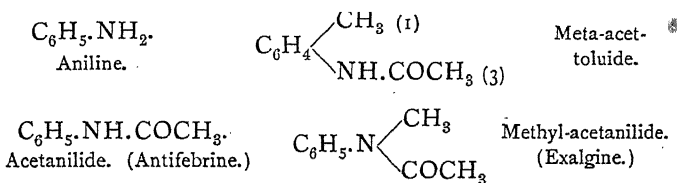
but it is not capable of effecting the hydrolysis of ethereal salts, so that the latter can be carried through the stomach unchanged into the intestine, a fact that has been taken advantage of in the preparation of such drugs as salol and bismuth and tannic acid compounds. Pepsin has little action upon drugs, but its functions may be affected by their introduction. The work of the pancreatic secretion in the duodenum stands in marked contrast to that of the gastric juice. The pancreatic juice is alkaline, its alkalinity, which is chiefly due to carbonate and phosphate of sodium, being equivalent to a 0.5 per cent. sodium carbonate solution; the other constituents include important ferments and the chlorides of sodium and potassium. The ferments, aided by the alkalinity of the secretion, are capable of decomposing ethereal salts; acids resulting from this decomposition are dissolved as salts, whilst the other constituents of the esters are separated in a soluble or insoluble form according to their nature. Such knowledge of the chemical action of the digestive juices has been of great value in localising the action of synthetically prepared drugs.

*Antipyretics derived from Aniline.*—Passing from these general considerations to the antipyretics derived from *aniline*, the base itself, as well as its salts, has marked antipyretic properties. They are, however, powerful poisons, being very readily absorbed by the system, and they decompose the hæmoglobin of the blood. By the substitution of a hydrogen atom of the amino-group, in bases, by an acid radical their toxicity is decreased, a fact which, as already stated, stands in an interesting relation to the discovery that certain organic compounds are eliminated from the system in combination with such groups. *Acetanilide*, the acetyl derivative of aniline,<sup>1</sup> is an example of this change in physiological properties; like aniline, it is an antipyretic, and being much less poisonous, it is admissible for therapeutic purposes. In addition to acting as a febrifuge, it possesses an anti-neuralgic action, and under the name of *antifebrine* is now largely used, despite the fact that like aniline itself it can give rise to bad secondary symptoms. The acetyl group is oxidised during the passage of the

<sup>1</sup> Cf. Chap. xi. p. 239.

drug through the system, so that its action may be regarded as that of a protracted aniline effect.

The physiological change produced by the introduction of a methyl group into acetanilide varies with the position it occupies. If a hydrogen atom in the benzene ring be substituted so as to form the acetyl derivative of toluidine, the meta-compound is the only one of the three position-isomers that preserves the antipyretic action of acetanilide; on the other hand, by substituting the hydrogen of the NH or imido-group, a compound is formed which, whilst its antifebrile action is much weaker than that of acetanilide, has a more marked analgesic or pain-relieving effect. Under the name of *Exalgine* it is employed as an analgesic, but care is required in its use, since it has been shown that it may produce bad secondary symptoms. The relations of these compounds are shown in the following formulæ:—



With the object of preparing drugs which, while of less toxicity than these simpler derivatives of aniline, should yet possess their antipyretic and anti-neuralgic properties, advantage has been taken of the observation that aniline, in its passage through the system, is partially converted into para-aminophenol. This compound is far less poisonous than aniline, a fact which is consistent with the general conditions of elimination of poisons; it is a powerful antipyretic but still retains, to some extent, the decomposing action of aniline upon hæmoglobin. The presence of an hydroxyl as well as of an amino-group in para-aminophenol allows of the preparation of numerous derivatives by the replacement of one or more hydrogen atoms by an alkyl or acid radical. There has been no lack of attempts to improve the therapeutic value of para-aminophenol by such substitutions; the derived products owe their action essentially to the contained aminophenol grouping, and it

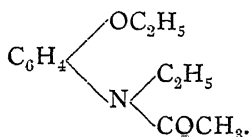
is characteristic of them all that they are eliminated in the urine as aminophenol or as its acetyl derivative, a change which is of value as a means of recognising an antipyretic or analgesic action in compounds derived either from aniline or from para-aminophenol.

The acetyl-derivative of para-aminophenol or hydroxy-acetanilide is less poisonous than aminophenol itself, but still too toxic for medicinal purposes. By the replacement of the hydrogen of the hydroxyl group by methyl the toxicity is decreased whilst the antipyretic and anti-neuralgic effects are increased; the ethyl homologue, *Phenacetine*, is still less poisonous, the antipyretic action is retained and the narcotic effect increased. Higher alkyls, such as propyl and amyl, decrease the antipyretic action. On the other hand, when the hydrogen of the imido-group is replaced by ethyl the antipyretic and narcotic effects, as well as the toxicity, are practically nullified, nor is any aminophenol eliminated when this derivative is administered. The physiological action of these compounds is, therefore, clearly connected with the presence of the  $\text{NH}.\text{COCH}_3$  group, associated with a benzene ring substituted by hydroxyl in the para-position. These relations are shown in the following table:—

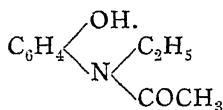
No.	Formula.	Nomenclature.	Toxicity.	Antipyretic action.
1	$\text{C}_6\text{H}_4 \begin{cases} \text{OH} \\ \text{NH}_2 \end{cases}$	1 : 4 Aminophenol.	Toxic.	Marked.
2	$\text{C}_6\text{H}_4 \begin{cases} \text{OH} \\ \text{NH}.\text{COCH}_3 \end{cases}$	1 : 4 Acetyl-aminophenol.	Much less than 1.	Similar to 1.
3	$\text{C}_6\text{H}_4 \begin{cases} \text{OCH}_3 \\ \text{NH}.\text{COCH}_3 \end{cases}$	1 : 4 Methoxy-acetyl-amino-benzene. ( <i>Methacetine</i> .)	Less than 2.	Greatest.
4	$\text{C}_6\text{H}_4 \begin{cases} \text{OC}_2\text{H}_5 \\ \text{NH}.\text{COCH}_3 \end{cases}$	1 : 4 Ethoxy-acetyl-amino-benzene. ( <i>Phenacetine</i> .)	Least.	Less than 3.

No.	Formula.	Nomenclature.	Toxicity.	Antipyretic action.
5	$\text{C}_6\text{H}_4 \begin{cases} \text{OC}_2\text{H}_5 \\ \text{NH} \cdot \text{COCH}_3 \end{cases}$	1 : 4 Propio-oxy-acetyl-amino-benzene.	Greater than 2 & 3.	Less than 4.
6	$\text{C}_6\text{H}_4 \begin{cases} \text{OH} \\ \text{N} \begin{cases} \text{C}_2\text{H}_5 \\ \text{COCH}_3 \end{cases} \end{cases}$	1 : 4 Ethyl-acetyl-aminophenol.	Nil.	Nil.

Similar studies have been made on the effect of replacing the hydrogen of the  $\text{NH} \cdot \text{COCH}_3$  group by alkyls, when that of the hydroxyl group is replaced by ethyl. Of these alkyl derivatives the methyl and ethyl compounds have the greatest antipyretic action, whilst the ethyl compound is the least poisonous. It is interesting to note that this substitution by ethyl does not annul the antipyretic properties as it does when the hydrogen of the hydroxyl is not replaced.



Ethyl-phenacetine.  
(Antipyretic.)



Ethyl-acetyl-aminophenol.  
(No antipyretic action.)

The outcome of these investigations has led to the recognition of phenacetine as the best antipyretic of this group. Both as a febrifuge and as a narcotic it is reliable and its very slight toxicity is much in its favour. One objection to its use is that it is only sparingly soluble. To overcome this defect other derivatives of para-aminophenol have been prepared, amongst which lactophenine and phenocoll deserve notice.

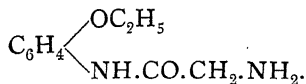
*Lactophenine* is a phenacetine in which the acetyl group is replaced by the radical of lactic acid,  $\text{CO} \cdot \text{CHOH} \cdot \text{CH}_3$ . It is more soluble than phenacetine, but the lactyl group is more easily separated by dilute acids than the acetyl



group, with the result that lactophenine is liable to undergo decomposition by the hydrochloric acid of the gastric juice in its passage through the stomach, giving rise to the formation of ethoxy-amino-benzene which has a poisonous effect. *Phenocoll* is amino-phenacetine, the amino-group being introduced into the acetyl radical; it forms readily soluble salts, and acts as an antiseptic in addition to being a febrifuge. Its antifebrile action is however too transient for therapeutic use, a fact which appears to be due to its rapid elimination by the kidneys.



1 : 4 Ethoxy-lactyl-amino-benzene.  
(Lactophenine.)



1 : 4 Ethoxy-aminoacetyl-amino-benzene. (*Phenocoll*.)

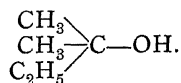
Many derivatives of diamino-benzenes and of phenyl hydrazine have been prepared on similar lines to the aminophenol compounds, with the object of obtaining antipyretics more soluble than phenacetine. No special interest attaches to the physiological properties of these compounds, nor have any of them proved to be of therapeutic value; they are stronger bases than the aminophenol derivatives, and this increased basicity is accompanied by an increase in their antipyretic effect, but also by increased toxicity.

## 2. NARCOTICS.

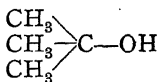
*Hypnotics and Anæsthetics. The Alcohols.*—Narcotics are substances which have the power of acting upon the nerve centres; they include anæsthetics and hypnotics. The aliphatic hydrocarbons have a narcotic action, and amongst their simpler derivatives a similarity in physiological properties is found to run side by side with an analogous structure. The primary aliphatic alcohols all have a toxic action, and their narcotic effects are greater than those of the corresponding hydrocarbons. Their chief action consists in paralysing the nerve centres, and this effect increases in intensity with an increase in the molecular weight of the alcohol until the solid alcohols are approached when, owing to their

insolubility and consequent too sparing absorption by the system, they cease to have any physiological effect.

Narcotics act upon the most highly organised nerve centres first, whilst the most simple and at the same time most automatic and stable centres are affected last. The order in which these nerve centres are rendered inactive differs amongst the various derivatives of the aliphatic hydrocarbons. Some induce sleep as the first result of their action, which only passes into anæsthesia when large doses are employed. Such substances are valuable as hypnotics; their action is weak but prolonged. Others act rapidly and more energetically, so that provided they are quickly eliminated and cease to act very shortly after being administered, they fulfil the conditions required by a good anæsthetic. Consequently, compounds of low molecular weight and high volatility are included in the latter group, whilst the former comprises substances having a relatively high molecular weight, and which are only slowly absorbed. This is illustrated in the hypnotic action of tertiary amyl alcohol, *Amylene hydrate*; it boils at  $102^{\circ}.5$ , and in doses of 2 grams produces sleep lasting from eight to nine hours. It passes through the system just as ethyl alcohol does, being converted into carbon dioxide and water. Its more prolonged action is to be traced to this decreased volatility and solubility; its hypnotic effect is also dependent upon the presence of the ethyl group since the corresponding methyl compound, tertiary butyl alcohol, is a far weaker hypnotic:—



Tertiary amyl alcohol.  
(*Amylene hydrate*.)



Tertiary butyl alcohol.

*Halogen Compounds.*—The halogen substitution products of the lower aliphatic hydrocarbons are characteristic anæsthetics, the well-known properties of *Chloroform* being shared by methyl chloride, methylene dichloride, and carbon tetrachloride. This narcotic effect is due to the introduction of the halogen; it increases with the number of chlorine atoms present, but the toxic effect also increases similarly. The volatility of methyl chloride has restricted

its use to that of a local anæsthetic; both *methylene dichloride* and *carbon tetrachloride* have been suggested as substitutes for chloroform, but they are less reliable than the latter.

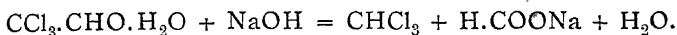
$\text{CH}_3\text{Cl}$ .	$\text{CH}_2\text{Cl}_2$ .	$\text{CHCl}_3$ .	$\text{CCl}_4$ .
Methyl chloride.	Methylene dichloride.	Chloroform.	Carbon tetrachloride.

The bromine derivatives of methane and its homologues also act as narcotics, and the use of *ethylene dibromide* ( $\text{C}_2\text{H}_4\text{Br}_2$ ) as an hypnotic and anti-epileptic has been suggested from the standpoint that the chronic poisoning effects that occur when potassium bromide is employed are due to the metal, and that this would be obviated by introducing the bromine in combination with a hydrocarbon residue, which would be oxidised in its passage through the body. Numerous other aliphatic bromine compounds have been prepared with this object in view; they all depend for their action on the liberation of bromine or of hydrobromic acid that takes place as they pass through the system, but this decomposition is too slow for them to compare with the inorganic bromides in their therapeutic value. The halogen derivatives of the aromatic hydrocarbons have no hypnotic properties.

*Aldehydes*.—The oxidation products of the alcohols, the *aldehydes*, preserve the narcotic power of the former, but they exercise an objectionable irritant action on the mucous membrane, especially in the case of the lower members. *Formaldehyde*, the lowest member of the group, presents, consistently with its chemical behaviour, some marked differences from its higher homologues. It is a powerful antiseptic and possesses the property of hardening the tissues; both as a preservative and as an antiseptic it is largely used, usually in a 4 per cent. aqueous solution, under the name of *formalin*.

*Acetaldehyde*,  $\text{CH}_3\text{CHO}$ , which contains an alkyl as well as an aldehyde group, acts as an hypnotic; its polymeric modification, *paraldehyde*,  $(\text{CH}_3\text{CHO})_3$ , is considerably less irritant in its action than the simpler molecule, but it has the disadvantage of possessing an unpleasant smell which it imparts to the breath and which is peculiarly adherent.

By substituting the hydrogen atoms of the methyl radical in acetaldehyde by chlorine the narcotic effect is much increased; the trichlor-substitution product *Chloral hydrate*,<sup>1</sup>  $\text{CCl}_3\cdot\text{CHO}\cdot\text{H}_2\text{O}$ , is a valuable and widely used hypnotic. Liebreich (1868) was led to the investigation of the physiological action of this compound from the consideration of its decomposition products by means of alkali. Chloroform and sodium formate result, even with very dilute alkaline solutions; chloral is readily absorbed by the system, and since, when absorbed, it enters the blood, which has an alkaline reaction, Liebreich expected it to be decomposed there into physiologically active chloroform and practically innocuous sodium formate, in accordance with the equation:—

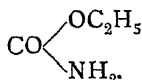


The utility of chloral hydrate as an hypnotic has been fully established, but the action is dependent upon the compound itself and not upon the formation of chloroform, as suggested by Liebreich's hypothesis. As previously stated, chloral hydrate is reduced to trichlorethyl alcohol,  $\text{CCl}_3\cdot\text{CH}_2\text{OH}$ , in the system; there is no decomposition into chloroform and sodium formate, and the trichlorethyl alcohol is finally eliminated in combination with glycuronic acid as a complex compound urochloralic acid,  $\text{C}_8\text{H}_{11}\text{Cl}_3\text{O}_7$ . Further, it may be stated that trichloroacetic acid, which also yields chloroform when treated with alkali, has no hypnotic action, whilst the above reduction product of chloral hydrate is itself an hypnotic, although much less powerful than chloral. The physiological action of this drug is therefore direct, and is to be attributed to the combined influence of the aldehyde group and the contained chlorine.

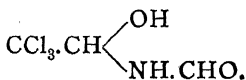
Whilst the introduction of chlorine into aliphatic compounds increases their narcotic effect, it is always accompanied by increased toxicity and by objectionable secondary effects upon the heart. This generality applies to chloral hydrate; it has a depressing action upon the heart and its application, therefore, becomes dangerous in cases of cardiac feebleness. Several attempts have been made to

<sup>1</sup> Cf. Chap. viii. p. 154.

improve upon chloral hydrate in this respect, by the introduction of certain radicals into this or analogous molecules, which should counteract the depressant action of the halogen atoms; the suggestions are interesting, but they have not led to the displacement of chloral hydrate as the most valuable of this group of hypnotics. The fact that ammonia has a stimulating action on the heart led Schmiedeberg (1885) to the preparation of *Urethane*, and the same idea has been followed in the case of chloral-formamide or *Chloralamide*; in both these compounds an amino-radical is present and as far as their cardiac action is concerned they may be said to possess the therapeutic properties indicated by theory. Urethane is a derivative of monoethyl carbonate in which an hydroxyl group is replaced by the amino-radical,  $\text{NH}_2$ ; it is a much weaker hypnotic than chloral hydrate, and has a slightly stimulating, instead of a depressant action. Chloral-formamide is derived from chloral hydrate by the replacement of one of the hydroxyl groups by  $\text{NH}_2$ , one hydrogen atom of the latter being further substituted by the radical of formic acid,  $\text{CHO}$ ; it is also a weaker hypnotic than chloral and possesses certain secondary properties of a disadvantageous character, of which the lowering of the body temperature is the most marked. Further, it is eliminated in the urine as urochloralic acid, the same product that is formed from chloral, so that its action is probably due to a gradual decomposition into chloral during its passage through the body.



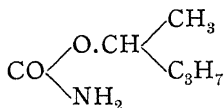
Urethane.



Chloral-formamide (Chloralimide).

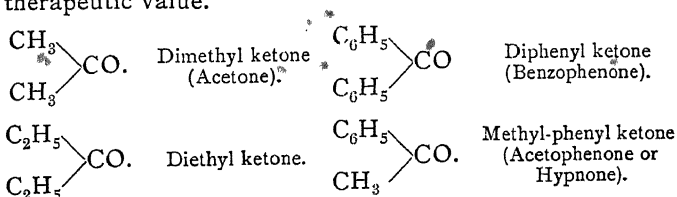
The hypnotic effect of urethane is essentially to be attributed to the presence of the ethoxy-group ( $\text{OC}_2\text{H}_5$ ), so that its action is to be compared rather with that of the alcohols than with that of the aldehydes. The physiological properties of its homologues and derivatives have been studied by Binet (1893), who has shown that the hypnotic effect increases with an increase in the molecular weight of the alkyl radical, amongst the lower members,

and that by replacing a hydrogen atom in the amino-group by acetyl, the physiological action is preserved whilst the toxic power is lessened. Amongst the homologues of urethane a substance known as *Hedonal*, in which the ethyl group is replaced by a methyl-propyl-carbinol radical, acts similarly to urethane but is a more powerful narcotic.



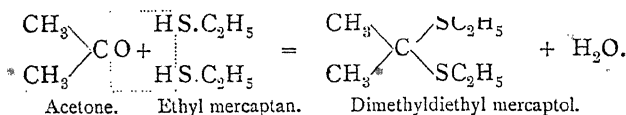
Secondary amyl urethane (*Hedonal*).

The *Ketones*, chemically so closely allied to the aldehydes, have also a narcotic action. The effect of the individual members of the group is to some extent dependent upon their molecular weight, but it is chiefly conditioned by the nature of the contained hydrocarbon radicals. The ethyl radical has the most marked effect; aryl radicals have little influence. Acetone or dimethyl ketone causes symptoms of intoxication, diethyl ketone acts as an hypnotic, benzophenone has considerably less narcotic effect than the aliphatic ketones, whilst the mixed ketone, acetophenone, has a stronger action and was suggested for use as a hypnotic under the name of *Hypnone*. None of these simpler ketones have, however, proved to be of any therapeutic value.

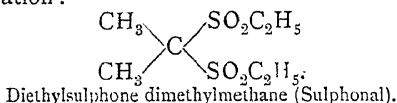


Amongst the hypnotics derived from ketones the *Sulphonal* group is the most important. A very complete series of investigations have been made by Baumann and Kast<sup>1</sup> on the physiological action of these compounds. They are derived from the aliphatic ketones by the action of mercaptans, the sulphur analogues of the alcohols, the products formed, which are called "mercaptols," being

subsequently oxidised. Sulphonal itself is thus prepared from acetone and ethyl mercaptan :—



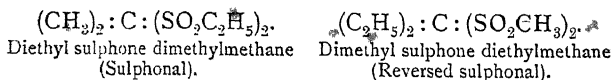
On oxidation :—



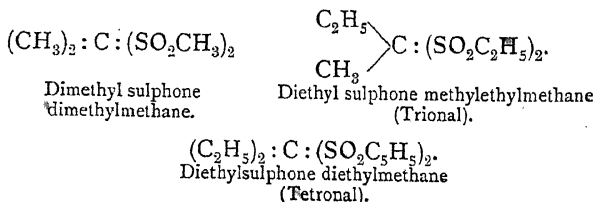
The oxidation, it will be seen, converts the  $\text{S.C}_2\text{H}_5$  group into the sulphone group,  $\text{SO}_2\text{C}_2\text{H}_5$ .

Sulphonal is recognised as a safe drug for inducing sleep, free from marked contra-indications and reliable in its action, except in respect to the time required for its effect to be produced which shows considerable individual variations. This last factor may be attributed to its being only slightly soluble and consequently slowly absorbed by the system.

The physiological effect of sulphonal is to be traced primarily to the ethyl groups present, and it is immaterial whether these are in combination with the sulphur atom or with the methane carbon of the molecule, for sulphonal and "reversed sulphonal" act similarly.



The sulphone with four methyl groups is quite inactive, whilst the triethyl- and tetra-ethyl- sulphones are more powerful narcotics than sulphonal.



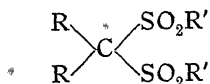
*Trional*, which is more soluble than sulphonal, acts more rapidly; *tetronal* is very difficultly soluble, but is the most powerful of these sulphone hypnotics.

The above examples show the association of the ethyl radical with the hypnotic effect of this group of compounds, but the action is also conditioned by the presence of the  $\text{SO}_2$  group in combination with a methane carbon atom, which is itself linked to one or two alkyl radicals. This statement is illustrated in the following table:—

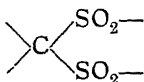
No.	Formula.	Nomenclature.	Hypnotic Action.
1	$\text{SO}_2(\text{C}_2\text{H}_5)_2$	Diethylsulphone.	Nil.
2	$\text{CH}_2(\text{SO}_2\text{C}_2\text{H}_5)_2$	Methylene diethylsulphone.	Nil.
3	$(\text{CH}_3)_2\text{C}:(\text{SC}_2\text{H}_5)_2$	Dimethyl-diethyl mercaptol.	Nil.
4	$(\text{CH}_3)_2\text{C}:(\text{SO}_2\text{CH}_3)_2$	Dimethylsulphone dimethylmethane.	Nil.
5	$\begin{array}{c} \text{H} \\ \diagup \\ \text{C}_2\text{H}_5 \end{array} \text{C}:(\text{SO}_2\text{CH}_3)_2$	Dimethylsulphone ethylmethane.	Slight.
6	$(\text{C}_2\text{H}_5)_2\text{C}:(\text{SO}_2\text{CH}_3)_2$	"Reversed" sulphonal.	Marked.
7	$(\text{CH}_3)_2\text{C}:(\text{SO}_2\text{C}_2\text{H}_5)_2$	Sulphonal.	Marked.
8	$\begin{array}{c} \text{CH}_3 \\ \diagup \\ \text{C}_2\text{H}_5 \end{array} \text{C}:(\text{SO}_2\text{C}_2\text{H}_5)_2$	Trional.	Greater than 7.
9	$(\text{C}_2\text{H}_5)_2\text{C}:(\text{SO}_2\text{C}_2\text{H}_5)_2$	Tetronal.	Greater than 8.



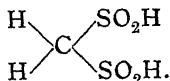
Only those substances (Nos. 5, 6, 7, 8, 9) which contain the group:—



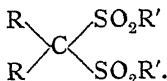
in which R and R' are alkyl radicals, and at least one of them an ethyl radical, are hypnotics; if one R group be replaced by hydrogen, a slight hypnotic effect is preserved. Or, the relations may be compared with the chromogen and chromophore groups of the organic dyes:—



Hypnotic group.



Mother substance.

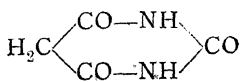


Hypnotic (in which R or R' must be  $\text{C}_2\text{H}_5$ ).

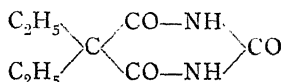
It is interesting to compare this marked influence of the ethyl group with that which obtains amongst other drugs. The characteristic action of the cupreine homologues is preserved irrespective of whether the substituting group is methyl or ethyl, and the same is the case in kind, though not in degree, with drugs of the antipyrine, aniline, and aminophenol groups, thus again showing that the specific influences of radicals is dependent upon the groups with which they are associated.

The study of the physiological action of a series of compounds of different chemical character to any of the narcotics described above led Emil Fischer and J. von Mering (1903) to the discovery of a valuable hypnotic in a urea derivative known as *Veronal*. This substance belongs to the group of the ureides, the condensation products of urea with acids, and which contain a heterocyclic ring, consisting of the urea residue in combination with an acid

radical; it is the diethyl derivative of malonyl urea or barbituric acid<sup>1</sup>:—



Malonyl urea.



Diethyl-malonyl urea (Veronal).

Inasmuch as it contains the residue of a urea molecule it bears some analogy to the hypnotics urethane and hedonal, whilst it resembles amylene hydrate and sulphonal in containing a central carbon atom attached to two alkyl groups and to two other stable radicals. These relations served Fischer and von Mering as a guide to the nature of the groups which they might expect to be of hypnotic value in a series of compounds. They accordingly prepared a number of closely related substances which allowed of a systematic comparison of the relative physiological effect of different hydrocarbon radicals and of open- and closed-chain derivatives of urea. This comparison has brought out many points of interest both in regard to the nature and power of the physiologically active groups.

A number of the substances examined are given in the following table, together with some data as to the rapidity and duration of their action as ascertained in experiments with dogs; the body weight of the animals was about the same in most of the experiments, so that the figures may be regarded as approximately comparative.

Contrasting the structure of veronal (No. 9) with that of the other compounds that precede it in the table, the influence of the two ethyl groups in combination with a urea residue is very marked. Neither the acid (No. 1) nor the amide (No. 2) have any hypnotic effect; each contains two ethyl radicals but no urea residue. It should be added that the carboxyl group characteristically inhibits physiological effects. Diethylacetyl urea (No. 3) contains the ethyl groups and a urea residue, and its action is definite though less prolonged than that of veronal, whilst the replacement of its hydrogen by carboxyl (No. 4) suffices to stay the hypnotic power altogether.

<sup>1</sup> Cf. Chap. ix. p. 178.

This illustrates well the marked effect of the carboxyl group, for this substance consists of a veronal ring broken by the addition of a molecule of water. The substitution of the two ethyl radicals by methyl (No. 5) eliminates the effect of the molecule, as in the case of sulphonal; the action is definite with one methyl and one ethyl radical (No. 6), but is again stopped when only one ethyl group is present (No. 7). This last fact is of considerable interest since it shows that the methyl radical when associated with ethyl has a contributory effect not possessed by the light hydrogen atom, although two methyl groups lead to an inactive compound; the methyl-propyl compound (No. 8) illustrates this same function of the methyl group. The remaining substances show the influence of the higher homologues of the ethyl radical; the hypnotic effect is increased by the propyl group (Nos. 10 and 11), but falls away with the heavier radicals isobutyl (No. 12) and isoamyl (No. 13). The dibenzyl compound (No. 14) is inactive, but this is probably on account of its sparing solubility.

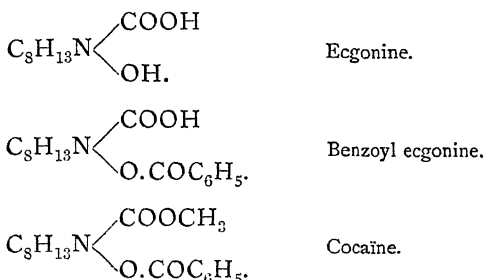
The hypnotic power of diethylacetyl urea (No. 3) approaches that of sulphonal, whilst dipropylmalonyl urea (No. 11) is approximately four times more powerful; the latter causes, however, at times a prolonged after-effect, and as veronal stands midway between these two compounds in its action it was selected as the most suitable substance of the group for therapeutic use. Veronal possesses a slightly bitter taste and is fairly soluble in water (1:145).

Subsequent investigations by Fischer and von Mering (1905) have shown that the dipropyl-compound possesses advantages over veronal for some forms of insomnia, and it has since been introduced for therapeutic use under the name of *Proponal*.

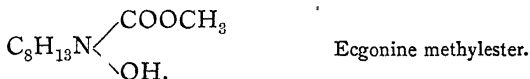
*Local Anæsthetics.*—The structure of the valuable local anæsthetic *Cocaine* having been established<sup>1</sup> some interesting points of comparison are available in respect to its physiological action. The alkaloid is obtained from the leaves of the coca plant (*Erythroxylon coca*), in which it is associated with several closely related compounds.

<sup>1</sup> Willstätter and Bode, *Berichte*, 1901, xxxiv. 1457.

It consists of a complex double ring, containing one nitrogen atom, and in which a benzoyl and a methyl radical are attached; the former replaces the hydrogen of an hydroxyl group, the latter that of a carboxyl group. These may be removed by the action of alkali, when a compound called ecgonine is formed, into which the benzoyl and methyl groups can be successively introduced to form benzoyl ecgonine and then cocaïne respectively. The relation of this base to benzoyl ecgonine and to ecgonine is shown in the following formulæ:—



Neither ecgonine nor benzoyl ecgonine possess the local anæsthetic action of cocaïne; nor has ecgonine methylester any anæsthetic effect.



The physiological action of cocaïne is, however, not particularly associated with the presence of the methyl radical, because if the hydrogen of the carboxyl group in benzoyl ecgonine be replaced by ethyl or higher homologues, the anæsthetic effect is preserved. The benzoyl group, on the other hand, cannot be replaced by other radicals, either aryl or alkyl, without practically destroying the specific therapeutic action of cocaïne, although benzoyl ecgonine is itself inactive. The toxicity and general physiological effect of drugs is always diminished by the presence of a free carboxyl group, as pointed out in connection with veronal, and the absence of any anæsthetic action in benzoyl ecgonine is to be attributed to this fact;

the action appears as soon as the acid group is converted into an alkyl ester. The anæsthetic properties of cocaine are consequently to be attributed to the ecgonine radical, in combination with the benzoyl group, with the free carboxyl group protected by an alkyl radical. It is probable that the alkyl group renders the initial absorption of the substance by the cell possible, that it serves as the "anchor," as with the methyl group in antipyrine, pyramidon, and quinine, and that the benzoyl ecgonine, as liberated from its ester, possibly as a result of dissociation, is the actual active principle of the drug. Similarly to the relations traced out in the case of sulphonal, ecgonine is the anæsthetic group, benzoyl ecgonine the mother substance of the drug, the esters of which are local anæsthetics.

This relation has led to the search for local anæsthetics amongst other analogous heterocyclic compounds and with some success, although no further special relations of structure to physiological action have been traced. *Tropacocaine* and *Eucaine* are the most valuable local anæsthetics that have been studied from these considerations. The former is chemically closely related to cocaine, the latter is derived from a complex condensation product of acetone and ammonia; both are less toxic than cocaine.

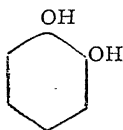
### 3. ANTISEPTICS.

*Phenol and its Homologues.*—Organic compounds having antiseptic properties are found chiefly in the aromatic group, and especially amongst those members of the group which contain the hydroxyl radical. *Phenol*, as is well known, is a most valuable and powerful antiseptic; it is also an irritant poison. The *Cresols*, the homologues of phenol, are less poisonous, and at the same time their antiseptic action is stronger. Their physiological effect differs according to the position of the substituting groups; meta-cresol has the most marked antiseptic effect, whilst the ortho-compound is less toxic than para-cresol. The slight solubility of the cresols rendered their practical application as antiseptics difficult, but it has now been found that they can be emulsified with various fats and soaps, and in this form many cresol preparations of varying purity, prepared from coal tar, are employed in anti-

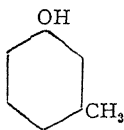
septic surgery, such as *lysol*, *creolin*, *solveol*, *solutol*, and Liebreich's *tricrosol*.

By further replacement of the hydrogen atoms in benzene by hydroxyl both the antiseptic and the poisonous properties are increased. The extent of the change again depends upon the relative position of the substituents. Of the dihydroxy-benzenes, catechol is nearly twice as toxic as quinol, whilst resorcinol is far less poisonous; of the trihydroxy-compounds, pyrogallol is twenty times more poisonous than its isomer phloroglucinol, and slightly more so than catechol.

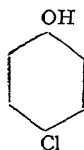
The halogen derivatives of the phenols are more powerful antiseptics and are less poisonous than the phenols themselves; of the mono-chlorphenols, the para-compound has the greatest antiseptic effect. From these examples of the physiological action of the position-isomers in the aromatic group it is clear that it bears no general relation to the orientation of such compounds; the maximum antiseptic action, for instance, occurs with the ortho-dihydroxybenzene, with meta-cresol, and with para-chlorphenol:—



Ortho-dihydroxybenzene  
(Catechol).



Meta-cresol.



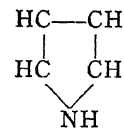
Para-chlorphenol.

*Iodoform and "Iodoform substitutes."*—Amongst aliphatic compounds the introduction of halogens is chiefly associated with an increase in their hypnotic properties, as already stated, but there are a few iodine derivatives of the aliphatic hydrocarbons which act as antiseptics, and of which *Iodoform*,  $\text{CHI}_3$ , is by far the most important. Owing chiefly to the marked and very penetrating smell of this valuable antiseptic, many attempts have been made to prepare odourless "*Iodoform substitutes*"; iodoform also has a further objectionable secondary effect inasmuch as it may at times be absorbed and give rise to toxic symptoms. A few of the proposed substitutes are of interest,

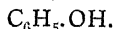
though none of them can be said to have replaced iodoform to an appreciable extent.

Although the antiseptic power of aromatic compounds is always increased by the introduction of one or more halogen atoms into the ring, the halogen is in too stable combination with the hydrocarbon radical for such compounds to be of value as iodoform substitutes. For it is recognised that the antiseptic action of iodoform is not a direct effect, but one that only becomes manifest in contact with tissues or tissue juices; hence, it is regarded as dependent upon the formation of decomposition products containing iodine, or upon the liberation of free iodine.

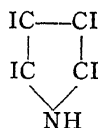
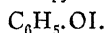
Tetra-iodopyrrole, or *Iodol*, the iodine derivative of pyrrole, in which the four hydrogen atoms of the ring are replaced by the halogen,<sup>1</sup> was the first iodoform substitute introduced; it has no smell, but owing to the greater stability of the contained iodine its antiseptic effect is far less than that of iodoform. Less stable iodine compounds are obtained from the benzenoid phenols by substituting the hydrogen of the hydroxyl group; they are called "iodo-compounds," and are readily decomposed with liberation of iodine, whilst they retain the antiseptic properties both of the phenols and the halogen. *Europhen* and *Aristol*, the di-iodo derivatives of di-isobutylmethylphenol and of di-thymol respectively, are the best of this group of substitutes. They are valuable both as antiseptics and as anti-syphilitics; they have no smell nor any toxic action, and their physiological effect is mainly to be attributed to the ease with which the contained iodine is liberated. The following formulæ illustrate the structure of these "iodoform substitutes":—



Pyrrole.

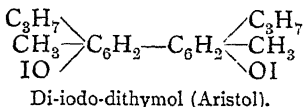
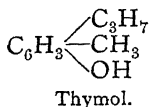
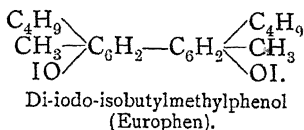
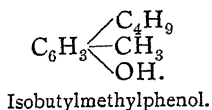


Phenol.

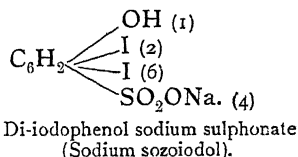
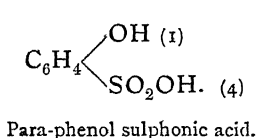
Tetra-iodopyrrole (*Iodol*).

Iodo-phenol.

<sup>1</sup> Cf. Chap. xv. p. 403.



Other halogen antiseptics, less toxic than the phenols, have been prepared from the consideration that the latter are eliminated from the system, chiefly in combination with sulphuric acid, as ethereal salts.<sup>1</sup> Phenol, for instance, forms phenylsulphuric ester, a small portion only being oxidised, chiefly to the dihydroxy-benzenes, catechol and quinol. The more stable sulphonic acids of the phenols are, like the closely related sulphates, both readily soluble and not poisonous; they pass through the system unchanged and hence serve as a useful starting point for the preparation of antiseptics from exactly those considerations which have been taken advantage of in the preparation of antipyretics derived from aminophenol. Their antiseptic power is less than that of the phenols, but by the substitution of hydrogen atoms by iodine or other halogens, this property is increased, whilst owing to the presence of the sulphonic acid group they are far less toxic than the simple halogen derivatives. *Sozoiodol* is the name given to one of the chief antiseptics of this group. It is para-phenol sulphonic acid, in which two hydrogen atoms are replaced by iodine; like all sulphonic acids it forms readily soluble salts with the alkalis.



The mercury and zinc salts of sozoiodol, both of which are

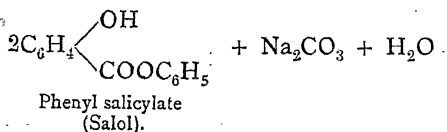
<sup>1</sup> Cf. *ante*, p. 453.



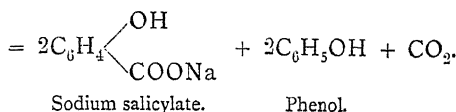
insoluble, have proved of considerable value as antiseptics, but their action is largely dependent upon the contained metal.

*Salicylic acid, Salol and the "Salol principle."*—A further group of antiseptics, with which other important physiological properties are associated, are derived from the aromatic acids. The introduction of the carboxyl group, as stated, decreases the toxicity of benzenoid compounds; benzoic acid is far less poisonous than benzene and the hydroxy-benzoic acids less poisonous than phenol. Of the three isomeric acids derived from phenol, the meta- and para-compounds have practically no physiological action; ortho-hydroxy-benzoic acid or *Salicylic acid*, on the other hand, whilst less toxic than phenol, is both an antiseptic and an antipyretic. The chief therapeutic use of salicylic acid, however, is due to its specific action against rheumatism; it is usually employed in the form of its soluble sodium salt. But the value of salicylic acid and its salts for this purpose is seriously diminished by the disturbance of the digestive functions which they may occasion; it was with the object of overcoming this objectionable secondary effect that Nencki (1886) was led to the preparation of *Salol*, and thereby to the introduction of an important fundamental principle in pharmacotherapeutics.

This *salol principle*, as it is generally called, consists in the administration of physiologically active compounds, such as salicylic acid, in the form of ethereal salts; such compounds, as already stated,<sup>1</sup> pass through the stomach unchanged, being stable towards the acid of the gastric juice, but on reaching the duodenum the contained ferments, aided by the alkalinity of the pancreatic juice, decompose them into their constituents. *Salol* is the phenylester of salicylic acid and its decomposition in the pancreas may be represented by the equation:—



<sup>1</sup> Cf. *ante*, p. 455.



Salol is, therefore, a chemical combination of two physiologically active compounds, which are regenerated by a definite function of the system; herein lies the value of Nencki's principle.

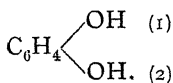
The decomposition of salol proceeds gradually, and the sodium salicylate, as liberated, is absorbed by the system; its anti-rheumatic effect should thus be obtained without any risk of disturbing the digestive functions. The phenol, similarly carried through the stomach in an inactive state, is set free just where it is valuable as an intestinal antiseptic, whilst owing to the gradual character of the decomposition its absorption by the system is less likely to give rise to poisonous effects than when administered directly. Salol has, as the result of extended experience, proved useful in both directions.

Another type of salicylic acid derivative is illustrated in *Aspirin*, a compound in which the hydrogen of the hydroxyl group is replaced by the acetyl radical. It retains the specific action of sodium salicylate against rheumatism, and has less irritant action.

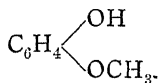


Very many similar derivatives have been prepared for use in medicine; it is easy to effect such combinations between a physiologically active phenol and an inactive acid, or the reverse, or to combine two physiologically active compounds, as in the case of salol.

*Guaiacol*.—Guaiacol carbonate is an example of the first of these methods of combination. Guaiacol is the methyl ether of the dihydroxy-benzene, catechol, which is both more poisonous and a better antiseptic than phenol; guaiacol is less toxic than catechol, a physiological change that is characteristic of the replacement of the hydrogen of the hydroxyl group of a phenol by an alkyl radical.

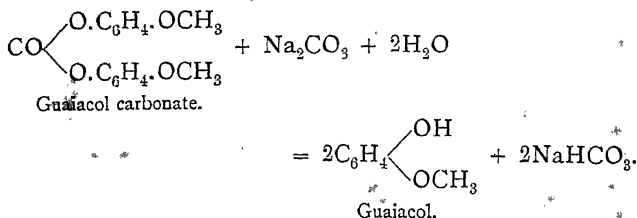


Catechol.



Guaiacol.

Sahli (1887) was the first to recognise that the value of creosote in phthisis was due to the contained guaiacol, and the latter is now largely used in the treatment of this disease. It has, however, an irritant action on the digestive functions, and with the object of overcoming this, ethereal salts, such as the carbonate, have been prepared for therapeutic use. Like salol, this carbonate passes through a healthy stomach unchanged, and is subsequently decomposed into physiologically active guaiacol and innocuous carbonic acid:—



The salol principle has also been successfully applied to the preparation of tannic acid derivatives, and of bismuth compounds; the former for use as astringents, the latter as intestinal antiseptics.

Whilst the chemical combination of physiologically active compounds, which are subsequently regenerated, has proved a most valuable therapeutic discovery, such combination is not always reliable in respect to the physiological action of the new compound. Glycerol nitrate (nitroglycerine) and tri-acetyl glycerol, for instance, both of which, as ethereal salts, are decomposed, similarly to salol, in the duodenum, have specific actions which are not shared by their constituents. Small doses of glycerol nitrate dilate the blood vessels, whilst tri-acetyl glycerol acts as a narcotic, and is distinctly poisonous, although neither glycerol nor acetic acid are toxic. Hence, in the preparation of compounds of this type

for therapeutic purposes, any specific physiological action they may possess must be carefully weighed and located.

Very many attempts have moreover been made to impart added therapeutic value to drugs by the combination of two physiologically active compounds, with the object of obtaining a resultant effect, either additive or the reverse. This method is in itself unscientific and haphazard. The specific physiological action of a compound is to be attributed to the presence of one or more groups, in association with a definite molecular structure, as already pointed out, and when two such compounds are combined chemically their resultant effect is, at most, the equivalent of that of a mixture of the two, whilst in many cases, owing to the elimination of certain radicals by the combination or to a change in physical properties, especially solubility, it is by no means the algebraic sum of the effects of the components. Chloral-hypnone, for example, a combination of the two narcotics, chloral and hypnone (acetophenone), has no narcotic action at all; iodo-antipyrine, which was prepared with the idea of obtaining a less toxic febrifuge than antipyrine, differs only in degree, but not in kind, from a mixture of antipyrine and iodine in respect to its physiological effect, and this difference in degree is entirely due to its being difficultly soluble and consequently sparingly absorbed by the system. With the object of decreasing the toxicity of phenetidine, para-ethoxy-amino-benzene, and also of increasing its solubility, certain combinations of this base with citric acid have been prepared; of these compounds some are decomposed by the acid of the stomach with the liberation of phenetidine, whilst others are so stable that they pass unchanged through the system, so that the antagonistic therapeutic effect expected has in no way been realised.

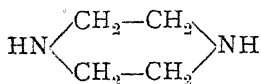
#### 4. OTHER SYNTHETICALLY PREPARED DRUGS.

Of the synthetical drugs not comprised in the three groups dealt with above, solvents for uric acid, purgatives and the sweetening compound, saccharine, are amongst the most important.

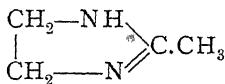
*Solvents for Uric Acid.*—Attempts have been made in two directions to combat the separation of uric acid which

accumulates in the system in gout and allied complaints. On the one hand it has been sought to decrease the formation of the acid and on the other to aid its elimination. The preparation of compounds with the former object in view, such as diphenyl tartrate and salts of quinic acid, has so far not been successful; the physiological requirements that must determine the selection or preparation of compounds to effect a decrease in the formation of uric acid are not yet known with sufficient accuracy.

The second method of attacking the problem, the preparation of uric acid solvents, has consisted in the application of non-toxic bases which form soluble salts with uric acid and thus should prevent its deposition in a similar manner to the treatment with salts of lithium, but with this in their favour, that they would be free from the injurious narcotic effects that may occur with the latter. Certain basic cyclic compounds of a somewhat complex character fulfil the necessary conditions outside the body; of these *piperazine* (the hexahydride of pyrazine<sup>1</sup>), and *lysidine* are the most important, both of which are heterocyclic substances containing two atoms of nitrogen, as shown in the following formulæ:—



Pyrazine hexahydride  
(Piperazine.)



Methyldihydroglyoxaline  
(Lysidine).

The necessity of recognising that the action of drugs within the system and without are two very different phenomena has been brought home most forcibly in connection with these uric acid solvents. Both lysidine and piperazine urate are much more soluble in water than lithium urate, but this advantageous solubility *in vitro* does not of necessity come into play in the system. Modern investigations on the nature and conditions of solution have thrown much light on resorption, secretion, the action of diuretics and other fundamental physiological

<sup>1</sup> Cf. Chap. xv. p. 408.

effects<sup>1</sup>; in respect to uric acid solvents they have also indicated new and important points of view. The solubility of a salt depends not only on its solubility in water or other pure solvent, but also upon the presence of other salts in the solution. The presence of a second salt, having a common constituent with the first, decreases the solubility of the latter; acid sodium urate, for instance, is nearly ten times less soluble in a salt solution containing seven grams of sodium chloride to the litre than in pure water. Other sodium salts cause a similar decreased solubility. Hence, the idea that the deposition of uric acid in the body can be prevented by the administration of large doses of sodium bicarbonate, owing to the formation of the more soluble, normal sodium urate is incorrect, and similarly, the hope to form soluble uric acid salts, by double decomposition of acid sodium urate with lithium salts, lysidine or piperazine, is based on a false view of the conditions of solution that obtain in the system.

The favourable action that lysidine and piperazine are said to possess requires an explanation other than that based on the solubility of their urates; it is possibly accounted for by their diuretic effect, the increased dilution of the urine being accompanied by an increase in the quantity of uric acid eliminated.

*Purgatives.*—The study of the chemical composition of vegetable purgatives such as rhubarb, senna, and aloes has shown that these products are glucoside derivatives of anthraquinone or are readily converted into closely allied derivatives of anthracene. This fact has led to the investigation of the purgative properties of anthraquinone derivatives. Many compounds of this group act as aperients, and their effect increases with the number of hydroxyl groups present in the molecule. The di-acetyl derivative of anthrapurpurin, a compound closely allied to alizarin,<sup>2</sup> but containing an additional hydroxyl group, is regarded as the most reliable of these compounds in its

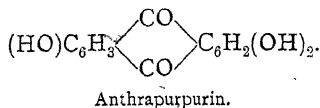
<sup>1</sup> Cf. *Physical Chemistry for Physicians and Biologists*, E. Cohen; trans. by M. H. Fischer, 1903.

*Physical Chemistry in the Service of the Sciences*, J. H. van't Hoff; trans. by A. Smith, 1904; Lectures VI. and VIII.

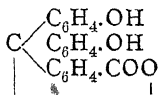
*Physical Chemistry in the Service of Medicine*, W. Pauli; trans. by M. H. Fischer, 1907.

<sup>2</sup> Cf. Chap. xv. p. 428.

action. It has the following formula, and has been introduced into medicine with some success under the name of "purgatin":—



A better synthetical purgative has recently been recognised in the well-known indicator phenolphthalein. The discovery of its value as an aperient is due to its having been employed to ear-mark, for administrative purposes, a certain kind of wine in Austria-Hungary, the addition of a small proportion allowing of the ready recognition of the wine by the characteristic, purple-red coloration produced on the addition of alkali. Although pharmacological experiments had previously shown that doses of phenolphthalein up to one gram per kilo body-weight had no effect upon animals, the consumption of the ear-marked wine soon showed that it had a purgative action on man, and further experiments have proved it to be a useful aperient both for children and adults. Phenolphthalein is very slightly soluble in water, but it dissolves readily in alkalis to form salts; it appears to have very little effect in the stomach, but on reaching the intestines it is converted by the alkali present into the readily soluble sodium salt to which the purgative effect is most likely due. There is little chemical analogy between anthrapurpurin and phenolphthalein beyond the fact that both contain hydroxyl groups, and both are closely related to organic dyes, the former to alizarin, the latter to the eosins. Phenolphthalein is a derivative of triphenylmethane, containing two hydroxyl and one carboxyl group, the latter being present in the form of an anhydride<sup>1</sup>; it has been introduced into medicine as "purgin":—



Phenolphthalein (Purgin).

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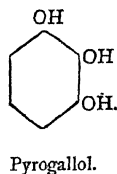
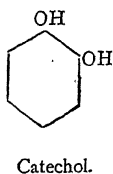
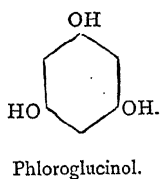
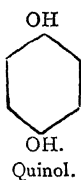
<sup>1</sup> Cf. Chap. xv. p. 422.

From a chemical standpoint the vegetable purgatives are amongst the most impure substances employed in medicine, and their substitution by synthetically prepared compounds is likely to lead to important practical results.

*The relation between Taste and Chemical Structure.*<sup>1</sup>—No relations of a very definite character have as yet been established between the taste and the chemical structure of organic compounds, and the discovery of substances having a sweet taste, such as saccharine and dulcin, has been quite accidental.

In the aliphatic group, an increase in the number of hydroxyl radicals is often accompanied by an increased sweetness in taste, as is shown by a comparison of alcohol, glycol, glycerol, and mannitol; the two last are distinctly sweet, whilst glycol is only slightly so and alcohol not at all. The sugars, such as grape sugar, are sweeter than the corresponding alcohols, so that an added sweetness occurs by the replacement of an alcohol by an aldehyde group; but this relation is by no means general, for in the di-hexose group,<sup>2</sup> cane sugar, which does not contain an aldehyde group, is sweeter than its isomers, maltose and lactose, which do. Derivatives of the sugars in which the hydrogen atoms of the hydroxyl groups are replaced by either acetyl or benzoyl radicals have either a neutral or a bitter taste, whilst those glucosides which are compounds of sugars with hydroxylic compounds, such as amygdalin and the tannins, are characteristically bitter.

In the aromatic group, the symmetry of the hydroxyl derivatives appears to be a determining factor in regard to their taste; thus, quinol and phloroglucinol are sweet, whilst the less symmetrical compounds, catechol and pyrogallol, are bitter.

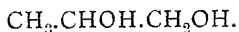


<sup>1</sup> Cf. W. Sternberg, *Geruch und Geschmack*, 1906.

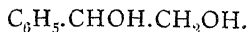
<sup>2</sup> Cf. Chap. xiii. p. 350.



Also, the substitution of an alkyl by an aryl radical causes a marked change in taste in several instances; dihydroxy-propane, for example, is sweet, whilst the corresponding phenyl compound (phenyl glycol) is bitter.

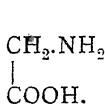


Dihydroxy-propane.

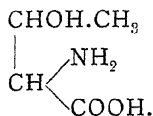


Phenyl glycol.

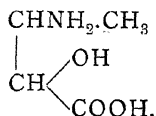
The amino-acids offer some interesting instances of a relation between taste and structure, as the presence of the two substituting groups appears to condition the property of taste, according to their relative position. Both amongst aliphatic and benzenoid compounds a sweet taste is most marked in those substances in which the two radicals,  $\text{NH}_2$  and  $\text{COOH}$ , are near to each other. Thus, amino-acetic acid (glycocoll) and  $\alpha$ -amino- $\beta$ -hydroxy-butyric acid are sweet, whilst  $\alpha$ -hydroxy- $\beta$ -amino-butyric acid, in which the amino- and carboxyl-groups are separated by an intervening carbon atom, is not.



Amino-acetic acid.

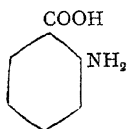


$\alpha$ -Amino-  $\beta$ -hydroxy-  
butyric acid.

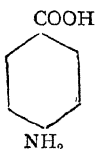


$\alpha$ -Hydroxy-  $\beta$ -amino-  
butyric acid.

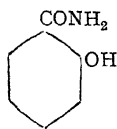
Similarly, ortho-aminobenzoic acid (anthranilic acid) is sweet, but the para-compound is tasteless; on the other hand, salicylamide, which is an ortho-compound, is tasteless, whilst the corresponding meta-compound is bitter.



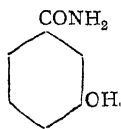
1:2 Amino-  
benzoic acid.



1:4 Amino-  
benzoic acid.

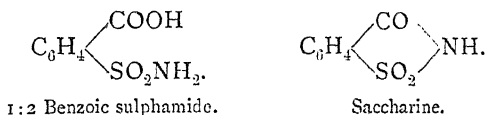


Salicylamide.



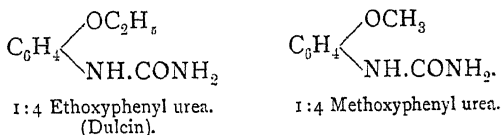
1:3 Hydroxy-  
benzamide.

*Saccharine*, which is some 400 times sweeter than cane sugar, is an amide derivative, being the anhydride of the amide of ortho-sulphobenzoic acid; the free acid (benzoic sulphamide) is not sweet.

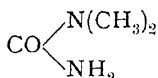


Saccharine possesses none of the physiological or preservative properties of sugar, and its medicinal value lies solely in its use as a sugar-substitute for diabetic patients; it passes unchanged through the body. The corresponding para-compound is not sweet, and ethyl-saccharine, in which the hydrogen of the imido-group, NH, is replaced by ethyl, is also tasteless.

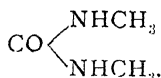
*Dulcin* is in no way related to saccharine in its chemical structure, but is allied to the aminophenol group of antipyretics, being the urea or carbamide of para-ethoxybenzene or phenetole. It is from 200 to 250 times sweeter than sugar, and like saccharine, is of no value as a food. The taste of dulcin is associated with the presence of the ethyl radical, for the corresponding methyl compound is not sweet.



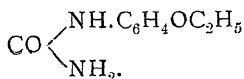
The symmetry of the molecule also appears to be related to the taste of such urea derivatives. The unsymmetrical dimethylurea, for instance, is sweet, whilst the symmetrical compound is tasteless, and a symmetrical analogue of dulcin, di-para-ethoxyphenylurea is also tasteless. In these cases the effect of molecular symmetry is, therefore, in an opposite direction to that with the hydroxy-derivatives of benzene,



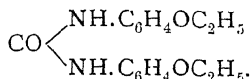
Unsymmetrical dimethylurea.



Symmetrical dimethylurea.



Dulcin.



Di-para-ethoxyphenyl urea.

The physiological action of many other groups of organic compounds including nitrites, nitrates, and purine compounds have been carefully studied. From a chemical standpoint the results are of a similar character to those detailed above.

Whilst it must be recognised that modern competitive conditions have led to an excessive supply of these new drugs, which has been detrimental to the interests of pharmaco-therapeutics, their preparation and the study of the relation of the structure of compounds to their physiological effect marks an important epoch in the services of organic chemistry.

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